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THE RATE OF SECRETION AND ELECTROLYTE CONTENT OF NORMAL GASTRIC JUICE

BY

BENGT NORDGREN

UPPSALA 1963

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THE RATE OF SECRETION AND ELECTROLYTE CONTENT OF NORMAL GASTRIC JUICE

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ALMQVIST & WIKSELLS BOKTRYCKERI AB

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FROM THE INSTITUTE OF PHYSIOLOGY, UNIVERSITY OF UPPSALA, SWEDEN

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INTRODUCTION

Most of our knowledge concerning the physiology of gastric secretion has been obtained in experiments on animals. This is especially true as regards quantitative studies. The reason for this has undoubtedly been the greater ease with which such experimentation can be performed on animals as compared to man. The need for quantitative data is great and the purpose of this investigation was therefore to study the following interrelationships in *man*:

(1) The injection rate of histamine and the rate of gastric secretion.
(2) The rate of gastric secretion and the concentrations of H^+, K^+, Na^+ and Cl^- in the secretion.

These relationships have been studied extensively in Heidenhain pouch dogs (for references see HEINZ and ÖBRINK, 1954). In man, however, only preliminary studies have been carried out (NORDGREN, 1958) and the data about these relationships in man are rather incomplete. The aim of the present study was therefore to acquire complementary data from human subjects without obvious signs of gastrointestinal or other disease. For comparison similar experiments were made on dogs with nearly intact stomachs (emptied through a fistula in the abdominal wall).

Notwithstanding the fact that there is a vast literature concerning the composition of the gastric juice in man, most of the studies reported were carried out with single subcutaneous doses of histamine or other stimulation procedures giving transient secretion values. To interpret such non-steady state values and especially to interrelate them is at present too difficult. In the present study care has been taken to try and keep all parameters at steady state levels thus avoiding the difficulties introduced by time lags and adjustment lapses. Details about the material and the methods used will be described in the relevant chapters.

MATERIAL

Five men in good physical condition were studied. For data about their physical status see Table 1.I. No symptoms of gastro-intestinal disease and no history of allergy were noted. In addition two dogs with gastric fistulae were used; these are also included in Table 1.I.

METHODS

Procedure

Dog experiments

A fistula was made in each dog by inserting a silver cannula in the lower part of the fundus of the stomach. The dogs were not used until four weeks after operation. The secretion from the stomach was collected via the cannula into a measuring cylinder, which was emptied at periods of about five to ten minutes. Before every experiment the dog was fasted for at least twelve hours but was allowed water. The animal was stood on a table and restrained in a loose harness. Each experiment lasted for about four to five hours. The histamine was injected continuously intravenously at a constant rate using a special injection device (see Öbrink, 1948). For concentrations and the volumes of the histamine injected see Table 1.I. To avoid side effects of histamine an antihistamine preparation, chlorpheniramine (Allergisan®, Pharmacia), was injected intravenously before the histamine (cf. Kay, 1953). The dose of antihistamine was four to twelve mg, the amount being adjusted for the injection rate of histamine.

In order to detect regurgitated material from the duodenum in the samples 0.1 – 0.2 gram of the dye uranine which is secreted in the bile, were injected intravenously in a single dose at the same time as the antihistamine.

Experiments in man

For purposes of comparison the procedure was as far as possible similar to that in the dog experiments. The gastric contents were removed at intervals of about five to ten minutes by suction through a rubber or a plastic tube. To prevent the swallowing of saliva this

was removed by a tube placed in the mouth. Before each experiment the subject had fasted for at least twelve hours but no restriction was placed on water intake. Each experiment lasted about three to five hours, and the subject sat leaning backwards in a comfortable chair. Each subject was used for several experiments. The injection procedure was the same as in the dog experiments. For doses and injection volumes see Table 1.I. The range of the dose of chlorpheniramine was 6 to 16 mg and of uranine 0.06 to 0.10 gram.

Analysis

Acidity

Two methods were used.

(*a*) 0.1 ml of sample was diluted with 4 ml of deionized water and titrated with 10 mN NaOH with bromthymolblue as indicator (pH-range 6.0–7.6). The NaOH solution was always checked daily against at least three 0.1 ml samples of 100 mN HCl (standard). The diluent water (4 ml deionized water) was also titrated on each occasion with NaOH to check that it contained no significant acidity. The standard error in the acidity determination was ± 1 mN.

(*b*) 1 ml of sample was titrated with Töpfers mixed indicator, dimethylamino-azo-benzene end point pH 3.5, for the free acidity; and phenolphthalein, end point pH 8.0, for the total acidity. The standard error was in these determinations $< \pm 1$ mN.

pH

pH was determined with a Radiometer pH meter, type phm 22 p using a glass electrode. The uncertainty was $+0.05$ pH units.

Chloride

0.2 ml of sample was titrated with 20 mN $Hg(NO_3)_2$ with 1 ml of citrate buffer (pH 1.5) and s-diphenylcarbazone (Eastman Kodak 4459) as indicator as according to Brun (1949). The $Hg(NO_3)_2$-solution was checked daily against a standard solution of 100 mN NaCl. The standard error in these determinations was ± 2 mN.

Sodium and potassium

Sodium and potassium were determined flamephotometrically. (Flamespectrophometers used were Perkin-Elmer Co. type 52A: Series 2, with internal lithium standard or Beckman B). Both sodium and potassium were determined in a concentration range up to 4 mN the samples being diluted when necessary. A calibration graph was made with standard solutions of KCl and NaCl (range 0.1–4.0 mN). Potassium does not interfere with the determinations of sodium in the presence of concentrations of at least up to 100 mN and the interference of 100 mN sodium on 1 mN potassium is only 5 % (MARSDEN, personal communication). Since the Na concentration when measuring K was never more than about 20 mN the sodium interference was neglected.

CHAPTER 1

The Relation between Injection Rate of Histamine and Gastric Secretion in Man and Dog

It is well established that after a subcutaneous injection of histamine the rate of gastric secretion first rises to a maximum and then declines until secretion finally ceases after about an hour. In studying the relationship between the dose of histamine and rate of gastric secretion this mode of histamine administration is unsatisfactory. It is desirable to obtain steady state conditions, i.e. to maintain a constant stimulus and thus a constant rate of secretion.

Teorell (1933) pointed out that a constant gastric secretory rate could be obtained by the continuous intravenous injection of histamine. In 1937 he presented the theoretical relationships between the injection rate and the concentrations of histamine in blood and tissue. He suggested that the steady state concentration should be directly proportional to the injection rate.

Öbrink (1948) confirmed the correctness of this hypothesis in studies on the concentration of histamine in plasma after continuous intravenous injection. He found a definite relationship between the injection rate of histamine and rate of gastric secretion for Heidenhain pouch dogs which could be described by the exponential equation.

$$v = a\,(1 - e^{-kr}) \tag{1.1}$$

where v = the rate of gastric secretion (ml/min),
r = the injection rate of histamine (mg/hour)
and a and k are constants.

Previously, only preliminary studies of this relationship have been made in man (Nordgren, 1958).

The purpose of the work, described in this chapter, was to study this problem in more detail with special reference to three parameters:

1. The maximal rate of gastric secretion
2. The sensitivity of the mucosa to histamine

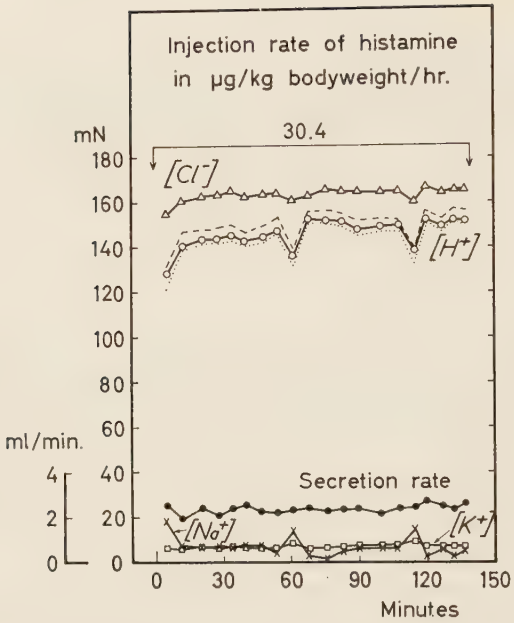

Fig. 1.1. A typical experiment with continuous intravenous injection of histamine and a steady rate of gastric secretion with fairly constant $[H^+]$, $[K^+]$, $[Na^+]$ and $[Cl^-]$. The $[H^+]$ was titrated with bromthymolblue (circles) in addition to Töpfer's reagent. Dashed lines, total acidity; and dotted lines, free acidity. (Dog M.)

3. The secretion in the absence of histamine stimulation (basal secretion).

In previous work on the human stomach or intact stomach in dog it has generally not been possible to assess the magnitude of admixture contributed by the saliva or duodenal contents. In the technique described here special attention has been paid to the presence of these disturbing factors.

Results

Dog experiments

The results of a typical experiment on a dog are shown in Fig. 1.1. It can be seen that the rate of secretion and the acidity $[H^+]$ reach a fairly constant level, which is maintained throughout the experiment, i.e. a steady state is obtained. A graph of the relation between

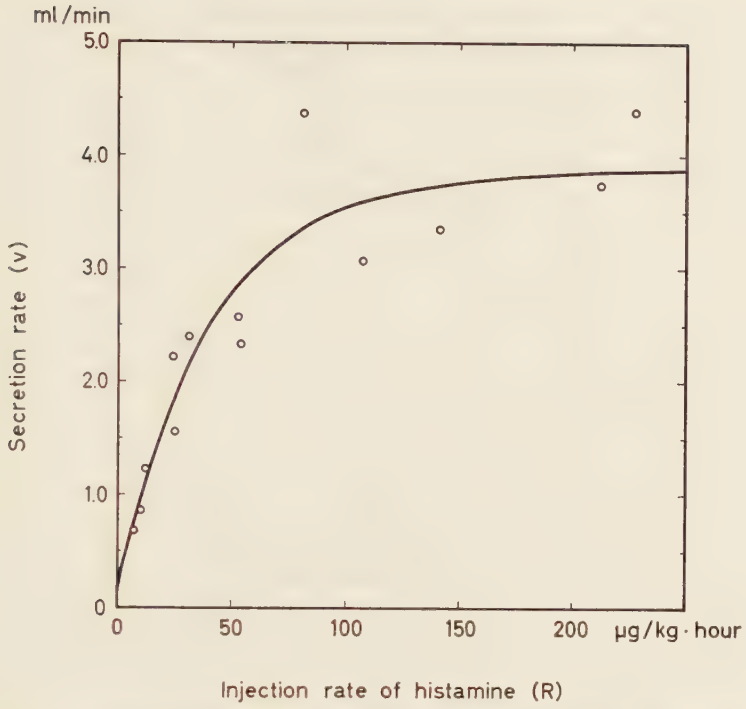

Fig. 1.2. The relationship between injection rate of histamine and rate of gastric secretion during steady state conditions. (Dog M.)

different steady injection rates of histamine, R (μg/kg body weight/hour), and the rates of secretion, v (ml/min), from different experiments on the same dog, is given in Fig. 1.2. Each point in Fig. 1.2 represents the mean secretion rate during the steady state in a single experiment (see Fig. 1.1). The continuous line was obtained by fitting the experimental values to Eq. 1.2 (see below) using the method of least squares.

Experiments in man

Fig. 1.3 illustrates a typical experiment on a human subject. With different injection rates of histamine correspondingly different rates of secretion were obtained. In experiments without histamine stimulation there was always a basal secretion. The results were expressed in the same way as in the dog experiments (see Fig. 1.4).

In order to evaluate the total loss of water during an experiment

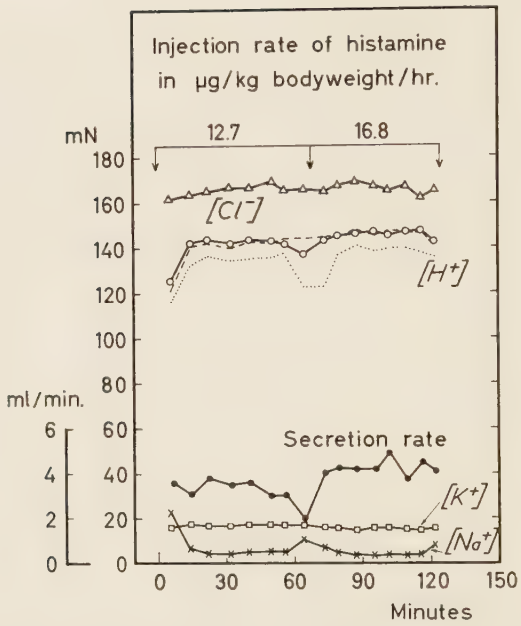

Fig. 1.3. A typical experiment in man. (Subject K. G. K.) The notation is the same as in Fig. 1.1.

the total amount of gastric contents and saliva collected from the subjects is shown in Table 1.I, where also the volume of saline injected along with the histamine is given. The total water loss was not determined in the dogs because it was considered that a salivary suction fixed in the mouth might be irritating. There was thus some additional unrecorded water loss due to salivary spilling from the mouth.

The juice collected might of course contain an admixture of saliva and duodenal secretion. In order to evaluate the extent of this contamination the procedure used in the experiments was found to be satisfactory for the following reason. Both the rate of gastric secretion and the acidity were obtained at steady state levels. An admixture of the gastric secretion of saliva or duodenal secretion increases the apparent "rate of secretion" but lowers the acidity (NORDGREN, 1958). A real increase in secretion rate is never accompanied by a decrease in the acidity and if this happens it must imply an extragastric admixture. Such an event is illustrated in Fig. 1.5 and it seems valid to exclude such values. If there was a sudden loss of gastric contents

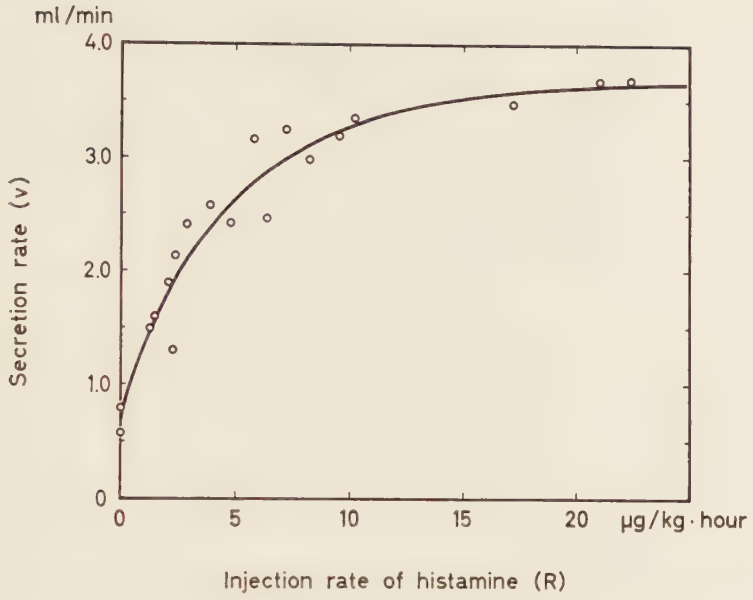

Fig. 1.4. The relationship between injection rate of histamine and rate of gastric secretion in man during steady state conditions. (Subject B. I.)

through the pylorus a steady secretion rate would be unlikely to be recorded. As a rule a steady rate was in fact observed.

Only those experiments, where steady state levels were attained, were included in the analysis of the results. In contrast to the experiments on man, contamination by large amounts of saliva and duodenal secretion in several dog experiments necessitated their exclusion from the acceptable material.

Some general comments on the results

The accuracy with which the gastric secretion rate can be measured is of great importance. For this reason special attention has been paid to the problem of contamination by the admixture of saliva or duodenal secretion.

Saliva

In addition to the saliva-sucker in the mouth (v.s.) a plastic tube connected to a suction device was in some experiments in man placed in the lower part of the oesophagus (about 40 cm from the teeth)

TABLE 1.I. *Data of the material.*

Subject	Weight kg	Length cm	Body surface[a] m^2	Age in years	Dose of histamine range $\mu g/kg \cdot hr$	Amount of fluid injected (ml)		Gastric contents withdrawn (ml)		Amount of saliva withdrawn (ml)		
						Mean	Range	Mean	Range	No. of experiments	Mean	Range
K. G. K.	77.0	190	2.04	26	3.1–21.1	12.9	9.5–15.5	422.8	259.7–578.5	5	337	220–537
B. I.	72.0	191	1.99	22	1.3–22.4	13.5	10.0–18.4	449.1	276.2–693.0	17[b]	208	95–420
H. C.	53.0	179	1.66	17	3.6–22.6	22.4	12.2–30.0	369.3	319.4–513.1	3	258	240–285
R. N.	51.5	—	—	15	3.7–20.1	16.2	10.0–24.9	506.3	319.2–687.1	5	209	155–370
G. L.	51.7	171	1.59	16	1.9–27.9	20.4	16.4–26.3	246.2	166.7–419.4	5	276	190–390
Dog L	22.5	—	—	—	7.0–36.3	12.2	5.6–19.1	271.8	161.7–458.5			
Dog M	19.2	—	—	—	6.8–227.3	12.7	9.6–22.5	369.6	127.7–581.8			

[a] Body surface calculated as according to DU BOIS and DU BOIS (1916).
[b] In 5 experiments the pH of the saliva was measured (mean 7.9, range 7.6–8.3).

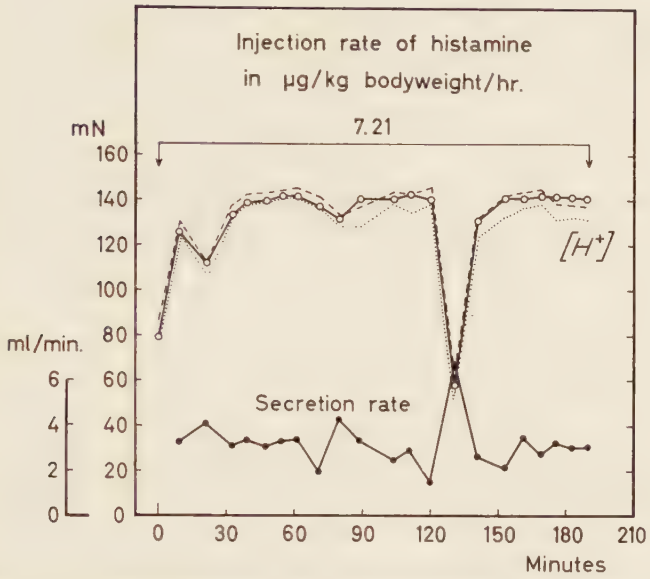

Fig. 1.5. An experiment in man demonstrating the occurrence of extragastric admixture. (Subject B. I.)

to remove saliva and possible oesophageal secretion. The largest amount collected during a 3 to 4 hours' experiment was not more than 3 ml, indicating that fluid movement between the mouth-oesophagus and the stomach (and the reverse direction) was negligible. It is shown in Table 1.I, that large amounts of saliva were collected through the mouth sucker during each experiment.

Duodenal regurgitation

To detect duodenal regurgitation a dye test was used (Nordgren, to be published). A number of different dyes were injected intravenously in cats during histamine stimulated gastric secretion. Of the dyes tested uranine was found most suitable because:

1. it gives an extremely intense colour, easily seen with the eye, and detectable photofluorometrically in concentrations of $1:10^7$;
2. it is not secreted by the gastric mucosa;
3. a considerable amount of the dye passes via the bile to the duodenum, and colours vividly all the duodenal contents;
4. it has a low toxicity (Fujii and Sakata, 1953).

TABLE 1.II. *Secretion rate and acidity before and after administration of chlorpheniramine.*

Subject	Dose of Allergisan given, mg	Secretion rate without Allergisan ml/min	Secretion rate without Allergisan % of a_1*	Secretion rate with Allergisan ml/min	Secretion rate with Allergisan % of a_1*	% difference of a_1 after Allergisan	Acidity [H+] without Allergisan mN	Acidity [H+] with Allergisan mN
H. C. (exp. 2)	12.0	1.27	37.6	1.37	40.5	+2.9	110	109
G. L. (exp. 5)	8.8	1.04	37.7	1.00	36.2	−1.5	96	95
R. N. (exp. 4)	12.0	0.31	9.7	0.34	10.6	+0.9	85	88
B. I. (exp. 11)	8.0	1.19	32.4	1.14	31.1	−1.3	100	106

*a_1 = maximal rate of gastric secretion.

Because of the appearance of some bile in experiment 11 (B. I.) this was not used when calculating the regression curve between the injection rate of histamine and rate of gastric secretion.

The appearance of uranine in the gastric contents was taken as evidence of duodenal regurgitation.

The effect of antihistamine on the gastric secretion

As chlorpheniramine was used to obviate the side effects of histamine it was of importance to exclude any possible effect of the antihistamine on the parameters under investigation. Chlorpheniramine (Allergisan®) in a dose of 8 to 14 mg therefore was administrated intravenously in a single dose during a period, when there was steady rate of fluid efflux from the stomach induced by continuous histamine injection. The secretory rate was kept below 40 % of the maximal theoretical rate of secretion in order to make the subject more sensitive to the possible effects of the antihistamine drug. At this level of gastric secretion, changes should exert relatively large effects on the secretory rate (Fig. 1.4). As can be seen in Table 1.II, only small changes were obtained after the administration of the chlorpheniramine. This is in accordance with many earlier reports (McELIN and HORTON, 1946; SANGSTER, GROSSMAN and IVY, 1946; MOERSCH, 1946; WOOD, 1948; RAGINS, BENDITT, GREENLEE and DRAGSTEDT, 1958), but it should also be noted, that a slight stimulating effect of the parenterally administered antihistamine has been reported (LINDE, 1950).

Discussion

The results indicate a correlation between the rate of gastric secretion and the injection rate of histamine in both man and the dog.

For the analysis of the dynamics of gastric secretion it is necessary to evaluate at least three parameters.

(i) The maximal secretory capacity (*MSC*), ml/min
(ii) An index of the sensitivity of the gastric mucosa to stimulation
(iii) The basal secretion rate, i.e. the secretion without histamine stimulation, ml/min.

Procedure for measurement of the parameters

The basal secretion was measured directly, but numerical values of parameters (i) and (ii) can only be calculated indirectly as follows:

The relation between the injection rate of histamine and the rate of gastric secretion in Heidenhain pouch dogs was found by Öbrink (1948) to be described by the equation:

$$v = a\,(1 - e^{-qR}), \tag{1.1}$$

where v = the rate of secretion (ml/min), R = the injection rate of histamine (mg/kg body weight hour, Öbrink used r), a = the maximal rate of secretion and q a constant (Öbrink used k). The locus of this equation is a line passing through the origin, which means that in the absence of histamine stimulation the rate of gastric secretion is zero. This is only a special form of the more general case where there is a basal secretion and which is described by the equation:

$$v = a_1 - a_2 e^{-qR}, \tag{1.2}$$

where v, q and R are the same as in Eq. 1.1, a_1 = the maximal rate of secretion (ml/min) and a_2 the maximal increment in the secretion rate obtained with histamine stimulation.

In the human subjects there was always a distinct basal secretion (v.i.), and therefore Eq. 1.2 has been used throughout this paper. No attempts were made to fit the experimental data to other types of equations, as Eq. 1.2 seemed satisfactory in most cases.[1]

[1] In calculating the regression line the total sum of squares is defined as

$$\sum d_2^2 = \sum (v_i - \bar{v})^2,$$

where v_i = the single observation of the rate of the gastric secretion, $\bar{v}$ = the

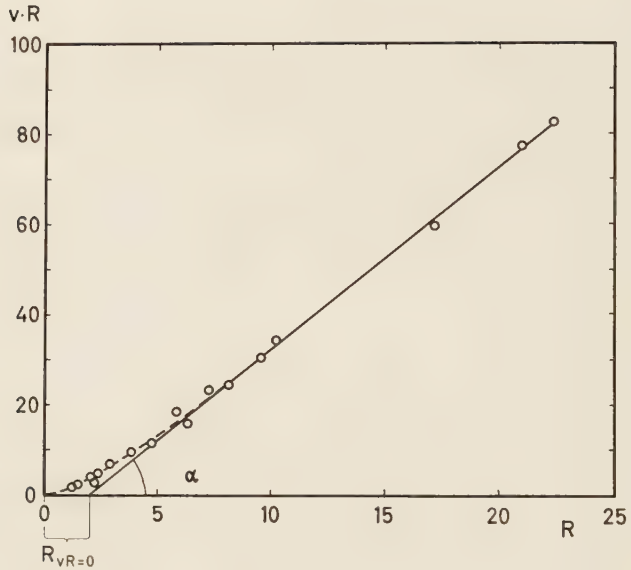

Fig. 1.6. The product vR plotted against v. The dotted line was obtained from Eq. 1.3. and the continuous line corresponds to Eq. 1.5. The slope of the continuous line is tan α and its intercept on the x-axis corresponds to $R_{vR=0}$. (Subject B. I.)

Discussion of an "approximation" test of the parameters

To determine the regression curve of Eq. 1.2 a considerable amount of experimental data is required; this introduces difficulties into its use in human physiology or clinical medicine. It might however be possible to characterize the stimulation–effect relationship on a basis of Eq. 1.2 by a more rapid estimation of the parameters in the following way. If both sides of Eq. 1.2 are multiplied by R we obtain

$$vR = R\,(a_1 - a_2 e^{-qR}) \qquad (1.3)$$

$$\text{or } vR = f\,(R)$$

mean of all v_i's. The residual sum of squares is defined as the sum of the squared deviations of the experimental points from the locus of Eq. 1.2. in which the parameters have been estimated according to the L.S. method. $1 - \sum d_1^2 / \sum d_2^2$ (where $\sum d_1^2$ is the sum of the least square distances of the experimental points from the regression line Eq. 1.2), can be used as reasonable measure of the degree of fit of the experimental points of the regression curve in the individual subjects (cf. for instance Snedecor, 1956). The expression $(1 - \sum d_1^2 / \sum d_2^2)$ may, however, be somewhat influenced by the numerical value of a_1.

Table 1.III shows that values of 100 $(1 - \sum d_1^2 / \sum d_2^2)$ up to 96 % were obtained. An analysis of the entire data using Eq. 1.2 is given in Table 1.IV.

TABLE 1.III. *The degree of fit with Eq. 1.2.*

Subject	No. of experiments	Σd_1^2	Σd_2^2	$100\left(1-\frac{\Sigma d_1^2}{\Sigma d_2^2}\right)\%$
K. G. K.	11	0.705	17.182	95.9
B. I.	17	0.986	9.629	89.8
H. C.	7	0.462	2.924	84.2
R. N.	5	0.637	1.117	43.0
G. L.	9	0.169	3.552	95.2
Dog L	8	3.391	8.611	60.6
Dog M	13	2.481	18.349	86.5

The product vR has been plotted against R in Fig. 1.6. Eq. 1.3 has an inflexion point (i.e. the second derivative = 0) at an R-value of $2/q$. Beyond the point of inflexion the curve rapidly tends to linearity (cf. Fig. 1.6).

The slope of the tangent at the point of inflexion is

$$\tan \alpha = f'(2/q) = a_1 + a_2/e^2. \tag{1.4}$$

The full equation of the tangent will consequently be

$$vR - f(2/q) - f'(2/q)\,(R - 2/q) = 0. \tag{1.5}$$

This gives an intersection on the R-axis

$$R_{vR=0} = \frac{4\,a_2}{q\,(a_1 e^2 - a_2)}. \tag{1.6}$$

The slope ($\tan \beta$) of Eq. 1.3 in the origin ($f'(R)$ for $R = 0$) is

$$\tan \beta = a_1 - a_2. \tag{1.7}$$

This slope was, however, difficult to evaluate graphically (see Fig. 1.6) and was therefore not used. But it should be remembered that $a_1 - a_2$ equals the basal secretion (b) that can be determined experimentally. Thus

$$a_2 = a_1 - b \tag{1.8}$$

If Eq. 1.8 is substituted in Eq. 1.4 and $\tan \alpha$ determined graphically, a_1 can be calculated. Knowing a_1, a_2 can be calculated from Eq. 1.8.

$R_{vR=0}$ in Eq. 1.6 can be determined graphically and in Eq. 1.6 q is now the only unknown parameter and can thus be evaluated.

The difficulty seemed to be to determine the slope of the tangent at the point of inflexion, but scrutiny of Fig. 1.6 shows that the bend of the curve at this point is so slight that the slope will be approximately the same even if it is not drawn through the point of inflexion.

A test was made to see how far from the point of inflexion in Eq. 1.3, the tangent could be drawn using the range of the R-values employed in the human subjects with varying q-values. Fixed a_1- and a_2-values (the mean of the calculated a_1 and a_2 respectively) were used with varying q-values inserted in Eq. 1.3. A low q-value gives the point of inflexion $(2/q)$ an R-value far greater than the experimental R-values. It can be shown that for q-values below 0.05 the graphical method gives an overestimate. Thus the construction of a tangent here could involve a rather uncertain extrapolation of the curve calculated from Eq. 1.3.

It is of interest to consider the information which can be elicited if for instance only two experimental points, as for example in a simple clinical test, are available. To examine this matter the positions of the tangents and R-axis intercepts ($R_{vR=0}$) drawn from any two points of a whole set of experimental points from the same individuals were estimated. The minimal distance between any pair of points used was 4.5 R-units and only points lying on or about the graph in its straight part were used. A typical set of such points is shown in Fig. 1.6. The entire material was treated in this way. The results show in the main reasonable accord (see Table 1.V) although some rather wide variations occur; in the latter cases, however, the degree of fit $(1-\Sigma d_1^2/\Sigma\, d_2^2$ in Table 1.III) was also rather poor. Obviously the more experimental points that can be determined the more accurate will be the values of tan α and $R_{vR=0}$.

The basal secretion rates were not included when the parameters in Eq. 1.3 were determined by the method of the least squares. For comparison the parameters were included in one subject (B. I.) including the basal secretion in Eq. 1.3, giving $q=0.20$, $a_1=3.72$, $a_2=2.98$, S (the standard error of estimate) $=0.26$ compared with $a_1=3.67$, $a_2=2.79$, $S=0.26$ (with the basal secretion excluded).

TABLE 1.IV. *The values of the parameters determined.*

Subject	No. of observations	Basal secretion mean	Calculations with the method of the least squares				a_1 per kg body weight	a_1 per m^2 body surface	Basal secretion in % of a_1	ED_{50} $\mu g/kg \cdot hr$ of histamine	Calculations with the graphical method	
			a_1 ml/min	a_2 ml/min	q kg · hr/μg	S					a_1 ml/min	q kg · hr/μg
K. G. K.	11	0.59	6.90	6.34	0.05	0.30	0.0896	3.38	8.6	13.8	5.47	0.09
B. I.	17	0.62	3.67	2.79	0.20	0.27	0.0510	1.84	16.9	3.5	3.62	0.22
H. C.	7	0.28	3.38	2.60	0.08	0.34	0.0638	2.04	8.3	9.2	3.11	0.11
R. N.	5	0.75	3.20	1.51	0.15	0.56	0.0621	—	23.4	4.7	3.06	0.17
G. L.	9	0.26	2.76	2.55	0.08	0.17	0.0534	1.74	9.4	10.0	2.39	0.10
Dog L	8	0.86	3.82	4.42	0.07	0.82	0.1698	—	22.5	15.0	4.50	0.44
Dog M	13	—	3.86	3.70	0.03	0.50	0.2010	—	—	28.0	—	—

Discussion of the various parameters

The basal secretion

In Heidenhain pouch dogs no basal secretion was found (Öbrink, 1948). In the present experiments in dogs with intact stomachs a basal secretion was not conclusively demonstrated. In man, however, the basal secretion does not cease even after extended fasting. Dragstedt, Oberhelman Jr. and Woodward (1951) suggested that the basal secretion was under central nervous control as it was markedly reduced after vagotomy.

In the present material there was considerable variation of the basal secretion rate in the same subject between different experiments. The mean values for each subject varied between 8 and 23 (mean 14) per cent of their corresponding *MSC* values. On account of the low acid output the acidity necessary to keep the pylorus closed may not always have been maintained. Some acid may therefore have been lost through the pylorus which could possibly explain some of the observed variations in the basal secretion rate.

The maximal secretion rate (a_1).

Several attempts to determine *MSC* with intravenous infusion of histamine have been reported. Öbrink (1948), Linde (1950) and Nordgren (1958) used Eq. 1.1 to calculate the *MSC*. Adams *et al.* (1954) calculated the *MSC* from a logistic curve after subtracting the basal secretion. Hansson *et al.* (1948) and Wood (1948) considered they had reached the *MSC* when a bigger dose of histamine gave no significant rise in output from the stomach. Table 1.VI gives a survey of the estimated values obtained from "steady state" conditions after histamine injection.

Even if it has not been proved rigorously that the acid originates from the parietal cells, there is much indirect supporting evidence. Thus Card and Marks (1957) in man and Marks, Komarov and Shay (1958, 1960) in dog reported a correlation between acid output and parietal cell mass. In patients with atrophic gastritis Guiss and Stewart (1948) found a relationship between the acid output and the estimated number of parietal cells left intact. Card and Marks (1960) in man also reported a correlation between the number of parietal cells in the excised part of the stomach and a diminished acid output. The frequency of parietal cells per unit area of gastric

Table 1.V. *The variation of tan α and $R_{vR=0}$ (Fig. 1.5.) when only two points along the slope are used to estimate them.*

Subject	The whole material used		Only two points used	
	tan α	$R_{vR=0}$	tan α	$R_{vR=0}$
K. G. K.	6.14	5.15	5.65	4.05
			5.92	4.80
			6.05	5.00
			6.35	5.90
			6.50	6.30
			6.70	6.10
			7.30	7.00
B. I.	4.03	1.90	3.95	1.50
			4.00	1.60
			4.08	2.10
			4.08	2.10
			4.10	2.20
			4.10	2.20
H. C.	3.50	4.10	3.87	3.70
			4.00	4.30
R. N.	3.38	2.20	2.95	1.40
			3.38	2.20
G. L.	2.68	4.20	2.46	3.70
			2.52	2.90
			2.64	4.30
			2.70	4.40
			2.74	4.90
			2.79	5.00
Dog L	5.06	9.20	3.40	−0.30
			4.47	8.40
			5.60	8.00
			6.17	10.00
Dog M	4.47	29.50	4.40	32.00
			4.55	37.00
			5.55	47.50
			6.10	63.50

mucosa was correlated to the acid output according to TONGEN (1950). Variations in the number of parietal cells may therefore be expected to be reflected by differences in the *MSC*.

Attempts to correlate *MSC* and weight or age of the subject were

TABLE I.VI. *Previous determinations of the maximal secretory capacity (MSC) in the whole stomach.*

Authors	Species	No. of subjects	Type of stomach preparation	Maximal secretory capacity (*MSC*)
Hansson, Grossman, Ivy (1948)	dog	6	total stomach vagally denervated	0.67–2.70 ml/min
Hansson, Grossman, Ivy (1948)	dog	4	intact stomach	1.15–1.70 ml/min
Hansson, Grossman, Ivy (1948)	man	1	intact stomach	4.75 ml/min (submax. capacity)
Nordgren (1958)	man	11	intact stomach	1.56–4.64 ml/min
Wood (1948)	cat	6	intact stomach	8.42 ml/hr

not successful (NORDGREN, 1958) nor could COX (1952) find any correlation between the weight or the surface area of the stomach and the body weight or the age.

Table I.IV shows the quotient between a_1 (the *MSC*) and the body weight or body surface. The body weight quotient was definitely bigger in the dogs than in man which may be a reflection of a bigger parietal cell mass per unit body weight in the dogs. In the present investigation the relation between *MSC* (a_1) and the body weight was found relatively constant and may therefore possibly be a rough measure of the magnitude of this quotient in a population of healthy subjects.

The "sensitivity index" q.

Measurements of the sensitivity of response of the gastric mucosa to stimulation are few (ÖBRINK, 1948, HUNT and KAY, 1954, NORDGREN, 1958). The *MSC* should be a measure of the number of parietal cells. However, it gives no information of the sensitivity of the parietal cells to histamine stimulation although this might be of equal or even greater importance than the *MSC* itself.

In this study a bigger q-value means that a lower injection rate of histamine suffices to produce the same relative rate of gastric secre-

tion (relative to the *MSC*). A suitable measure of the sensitivity would therefore seem to be the injection rate of histamine evoking 50 % of the maximal rate of secretion. This injection rate might be called the Effective Dose 50 (ED_{50}), (see Table 1.IV). ED_{50} can be determined if the parameters a_1 and a_2 of Eq. 1.2 are known and $ED_{50} = 0.693/q$, i.e. ED_{50} is in fact independent of a_1 and a_2. It can also be determined from the sigmoid relation between the dosage of histamine (log R) and the rate of secretion.

A high numerical value of q (i.e. a low value of the ED_{50}) indicates a high sensitivity of the gastric mucosa to histamine. The term "*hypersecretion*", a word often used in a rather vague way, might therefore be defined more quantitatively in terms of a high q (or a low ED_{50}) value or a high *MSC* value, or a combination of both. Hypersecretion would thus refer to the sensitivity of the response of the gastric mucosa to a submaximal (e.g. 50 %) histamine stimulus, as well as to the magnitude of the maximal secretory rate which is correlated with the number of parietal cells.

CHAPTER 2

The Relation between the Rate of Gastric Secretion and the Acidity during Steady State Conditions in the Intact Stomach of Man and Dog

The existence of a simple relationship between the rate of gastric secretion and acidity has been a matter of much discussion. HOLLANDER and GOWGILL (1931) found that when a single massive dose of histamine was given subcutaneously the acidity rose and remained at a constant level for a rather long time, while at the same time the secretion rate reached a peak and then declined again. This seemed to contradict the existence of a simple relationship, but GRAY, BUCHER and HARMAN (1940), who injected histamine subcutaneously every 10 minutes into dogs, obtained a constant rate of gastric secretion and suggested there was a hyperbolic relationship between the rate of gastric secretion and the acidity.

A prerequisite for proving a fixed relationship seems to be a constant secretion rate.

ÖBRINK (1948) in Heidenhain pouch dogs and NORDGREN (1958) in man studied the rate of secretion and the acidity with continuous intravenous injection of histamine. ÖBRINK (1948) found that the following relation fitted well with the experimental data.

$$H = \frac{C_0}{\frac{k}{v} + 1}, \tag{2.1}$$

where H = the observed acidity (mN),
C_0 = the primary acidity (mN),
v = the secretion rate (ml/min) and
k = a permeability coefficient (ml/min)

Eq. 2.1 was deduced by TEORELL (1947) from his "diffusion theory" which thus found experimental support. In the "diffusion theory" he suggested that the diffusion of hydrogen ions and other electrolytes

through the mucosa (i.e. back diffusion of H^+ from the stomach to the circulation) causes the changes in the concentrations of the electrolytes observed at different secretion rates.

"The primary acidity"

The "primary acidity", C_0 (i.e. the acidity which the parietal cell is postulated to secrete), was studied through instillation of a buffer, glycine, into the stomach, thus reducing backdiffusion of H^+ from the stomach. In cats TEORELL (1940) calculated C_0 to be 208 mN and in dogs LINDE, TEORELL and ÖBRINK (1947) calculated the C_0-value to be 169 mN rising to 464 mN with diminishing rate of gastric secretion. Their highest analytical value was 354 mN. In man IHRE (1938) got a value of 143–145 mN and KAIJSER (1943) a maximum of 155 mN when determining C_0 with glycine instillations. On account of difficulties in avoiding extragastric admixture and losses of glycine the results in man must be considered as somewhat uncertain.

The *necessity of constant secretion rates* when analysing the present relationship should be stressed. In non-steady states time lags obscure the relations, cf. ÖBRINK's "lake hypothesis" (1948).

The relationship has been thoroughly investigated only for gastric pouches, and there is a dearth of information from *intact stomachs*. The purpose of this investigation was therefore to study the relationship between the rate of gastric secretion and the acidity in man and dog. Continuous intravenous injection of histamine was used to get steady state conditions necessary for quantitative analysis of the relationship.

Results

Dog experiments

In Fig. 1.1 a typical experiment is shown. When the rate of secretion is constant, the acidity also becomes constant. The relatively small amounts of "bound acid" determined through titration with Töpfer's reagent indicate that there are practically no weak acids or buffering substances in the secretion. In Fig. 2.1 the steady state acidity levels are plotted against the corresponding rates of secretion (v) obtained in every such experiment. The regression curves were

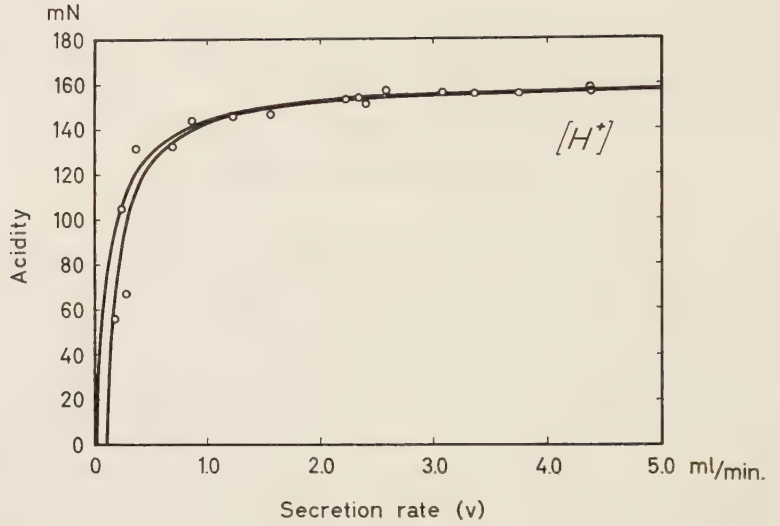

Fig. 2.1. The relationship between rate of gastric secretion and acidity (titrated with bromthymolblue) during steady state conditions. The left curve in the figure was obtained from Eq. 2.1 and the right curve from Eq. 2.2. (Dog M.)

obtained by using the method of the least squares on Eq. 2.1 (the left curve) and on Eq. 2.2 on the right curve respectively (see below).

Reduction of extragastric admixture with drugs.

In both man and dog, in experiments with low rates of gastric secretion, extragastric admixture was sometimes a serious source of error and thus a steady gastric secretion rate could not always be obtained. In order to diminish the possibilities of extragastric admixture in the gastric secretion by the saliva, bile and pancreatic juice, the following inhibitory drugs were given in some experiments: Propantelin (Probanthine®, Searle), total dose 6.0–13.5 mg or Dixamon (Banthine®, Searle), total dose 20.0–32.5 mg. They were given as single intravenous doses during the first part of the experiments.

These inhibitory drugs also to a certain extent inhibited the histamine stimulated gastric secretion, so that a lower rate of gastric secretion was obtained compared to when the drugs were not administrated. The relationship between acidity and secretion rate during steady state might possibly be somewhat disturbed in the same way, as Nordgren and Öbrink (1956) showed that atropine caused an increased acidity for a fixed secretion rate, but such a disturbance was

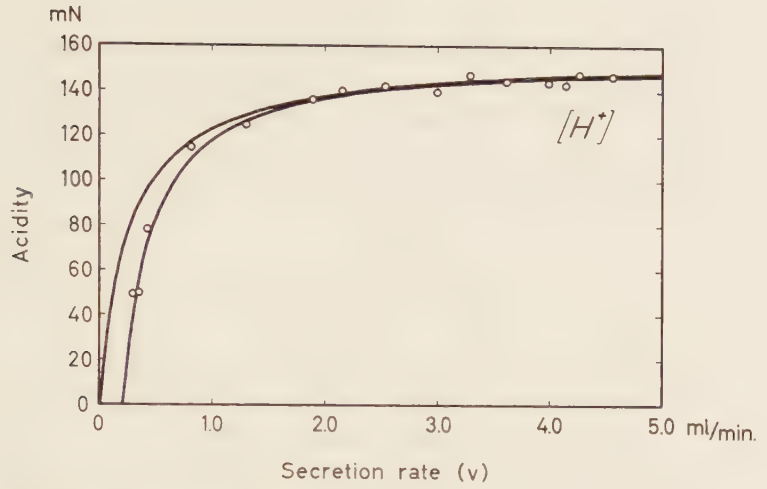

Fig. 2.2. The relationship between rate of gastric secretion and acidity in man. (Subject K. G. K.) Further see legend of Fig. 2.1.

probably of less significance than that of extragastric admixture. An example of this is seen in Fig. 2.2, where of the two points with the lowest acidity one is obtained with and the other without injection of an antisecretory drug.

Experiments in man

Fig. 1.3 illustrates a typical experiment. As in the dogs only a small amount of "bound acid" was present. In Fig. 2.2 the steady state values of the acidity from the same subject (K. G. K.) are plotted against the corresponding gastric secretion rates.

Discussion

The quantitative relationship between rate of gastric secretion and acidity in man and dog with intact stomach was determined.

Correlation to the theoretical relation used

In Figs. 2.1 and 2.2 it can be seen that the experimental points fit rather well with the regression curves. The left curve in the figures

was obtained when using the method of the least squares on Eq. 2.1. Eq. 2.1 postulates the complete and immediate mixing of the acid secreted. With this condition TEORELL (1947) regarded the concentration gradient between the gastric acid secreted and the blood as $[H^+]-0$. If, however, mixing is incomplete the concentration gradient will be maximally C_0-0 instead of $[H^+]-0$. ÖBRINK (1948) treated this case and derived the equation

$$H = C_0 \left(1 - \frac{k}{v}\right). \tag{2.2}$$

The symbols are the same as in Eq. 2.1.

As can be seen from Figs. 2.1 and 2.2, Eq. 2.2 seems to fit slightly better than Eq. 2.1 indicating the existence of some degree of incomplete mixing of the acid secreted.

In Table 2.I the primary acidity (C_0) and the permeability coefficient (k) were determined for the whole material using both Eqs. 2.1 and 2.2. The sum of the least squares was used to indicate which equation fitted best.

Graphical determination of the primary acidity and the permeability coefficient

For the graphical determination of C_0 and k which is a quicker procedure, the product vH (i.e. the acid output per minute) was plotted against v (Fig. 2.3), cf. ÖBRINK (1948) and HEINZ and ÖBRINK (1954). The dotted curve in Fig. 2.3 was derived from Eq. 2.1 and can be written

$$vH = vC_0 - kH \tag{2.3}$$

(with the same symbols as in Eq. 2.1).

Similarly Eq. 2.2 gives (both sides multiplied by v and rearranged)

$$vH = vC_0 - kC_0 \tag{2.4}$$

This is the straight line of Fig. 2.3 (C_0 and k are assumed to be constants).

For high values of v Eq. 2.3 and Eq. 2.4 will be almost identical because

$$kH = kC_0 \tag{2.5}$$

when $v \to \infty$.

TABLE 2.I. *Data and calculated parameters of the acidity secretion rate relationship.*

Subject	Number of experiments	Calculations with the method of the least squares						Graphical calculation		[H+] at v 2.5	Highest [H+] measured at the titration mN
		$H = C_0\left(1 - \frac{k}{v}\right)$			$H = \frac{C_0}{\frac{k}{v} + 1}$						
		C_0 mN	k ml/min	S	C_0 mN	k ml/min	S	C_0 mN	k ml/min		
K. G. K.	15	153.4	0.22	9.0	158.0	0.35	11.2	152.5	0.22	139.5	149.0
B. I.	18	154.3	0.31	7.9	157.5	0.42	11.7	154.0	0.30	135.0	145.0
H. C.	10	140.8	0.19	9.3	153.1	0.43	7.6	150.0	0.33	130.0	139.0
R. N.	12	126.3	0.24	17.0	130.3	0.38	20.5	140.0	0.51	114.0	129.0
G. L.	13	138.0	0.23	9.2	153.4	0.52	25.4	148.0	0.34	127.0	127.0
Dog L	8	162.1	0.25	21.4	161.0	0.26	24.0	166.0	0.34	146.0	162.0
Dog M	17	160.9	0.11	3.5	162.2	0.14	5.9	161.5	0.15	154.0	161.0

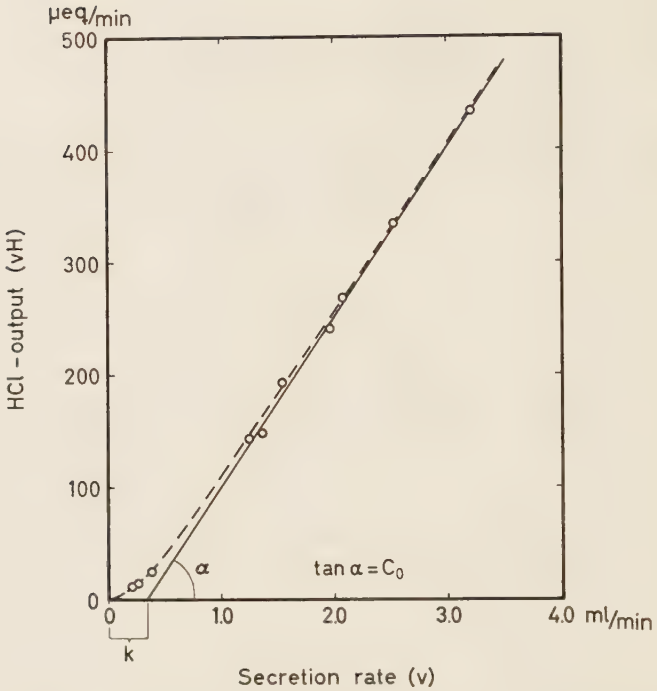

Fig. 2.3. Rate of gastric secretion plotted against acid output per unit time. The dotted curve represents Eq. 2.3 and the continuous line Eq. 2.4. Tan α in the figure then equals C_0 and the x-axis intercept of the Eq. 2.4 is equal to the permeability coefficient k. (Subject H. C.)

When applying this graphical method the experimental data always lay along a straight line if the v-values were above 1 ml/min. It would seem valid to regard the straight part of Eq. 2.3 in Fig. 2.3 as an approximation to Eq. 2.4. The slope from the straight line would represent C_0 and the intercept of the line on the x-axis would be k. Table 2.I shows C_0 and k calculated graphically in this way.

Use of an "approximation" test for determination of C_0 and k

In order to determine whether it is possible to evaluate C_0 and k approximately from only two experimental points, pairs of points one in the highest secretion range and the other at a secretion rate just above 1 ml/min, were used (Table 2.II), this table gives the minimum

TABLE 2.II. *The primary acidity, C_0, and the permeability coefficient, k, calculated from the "approximation" test proposed. The meaning of "Range v" and "Range vH" is described in the text.*

Subject	C_0 mN	k ml/min	Range v	Range vH
K. G. K.	152	0.21	1.89–4.26	256–630
	154	0.25		
	157	0.25		
	157	0.27		
B. I.	154	0.31	1.50–3.68	181–512
	151	0.24		
	153	0.30		
	149	0.23		
H. C.	155	0.41	1.27–2.52	150–330
	149	0.30		
	160	0.44		
	152	0.32		
R. N.	135	0.53	1.72–2.49	256–314
	126	0.35		
	150	0.62		
	139	0.43		
G. L.	163	0.47	1.08–2.15	98–258
	156	0.39		
	150	0.42		
	143	0.33		
Dog L	173	0.39	1.92–3.40	284–494
	164	0.18		
	148	0.15		
	133	−0.23		
	162	0.29		
	146	0.02		
Dog M	163	0.16	1.55–4.37	227–683
	163	0.13		
	160	0.13		
	158	0.10		

and maximum distances (range) between the pairs of points on the x-axis (v) and the y-axis (vH). With few exceptions the values in Table 2.II agree rather well with the corresponding values in Table 2.I.

The primary acidity

From Table 2.I it can be seen that in man the primary acidity, C_0, is lower than in dogs. Before accepting this as true all possibilities that it is an artifact resulting from the experimental or other conditions must be ruled out.

The parietal cells are assumed to be the acid secreting cells. They are found over the greater part of the body of the intact stomach, but the pyloric part (here estimated to contain maximally 20 % of the total surface) lacks them (Berger, 1934; Cox Jr., 1952) and has no acid secretion. This means that in the body of the stomach both secretion and back diffusion of H^+-ions take place, while in the pyloric part only back diffusion is possible. With incomplete intragastric mixing the amount of acid stored in the pyloric part and the time for this storage would be important. In the dog experiments the acid gastric contents were emptied continuously, while in man the gastric juice remained in the stomach for some minutes.

Teorell (1939) instilled HCl into the resting stomach of cats and measured the rate at which H^+-ions disappeared. As there was no acid being secreted into the stomach the relationship

$$H = H_0 e^{-kt/p} \tag{2.6}$$

described the results well which fits the concept of diffusion with a concentration gradient $[H^+] - 0$ between gastric juice and blood.

H = the concentration at time t,
H_0 = initial concentration at the beginning ($t = 0$) of the instillation,
k = the permeability coefficient (ml/min),
p = the volume instilled (ml) and
t = time (min)

The juice secreted into the human stomach remains there until the next emptying. During this time it should be expected that in the pyloric part the acidity will be reduced as according to Eq. 2.6. The final acidity after such an "instillation" can be estimated as follows: At the highest secretion rates the acidity will be approximately C_0. Applying Eq. 2.6 H_0 should thus be equal to C_0. In this discussion we assume both dog and man to have the same value of C_0 (162 mN).

The stomach was emptied at intervals not longer than about ten

minutes and it is assumed that the juice collected was secreted continuously during this period. This makes it possible to estimate roughly the values of p and t in the following way.

The volume secreted during the first minute has on an average remained in the stomach for $9\frac{1}{2}$ minutes, while the volume secreted during the tenth minute has remained for a half minute. The whole volume secreted during 10 minutes can be considered to have been instilled during approximately 5 minutes. This whole volume constitutes the p and will here be 10 a_1 ml (cf. Eq. 1.2). The permeability coefficient k was shown in cats (KAIJSER, 1943) not to differ significantly between the equally divided upper and lower parts of the stomach. 20 % of the surface of the stomach mucosa (the pyloric part) gives $k/5$. The mean k-values from Eq. 2.1 and Eq. 2.2 were determined for each man (see Table 2.I).

The values for H_0 (C_0, mN), p ($10a_1$, ml), t (5 min) and k can now be inserted in Eq. 2.6.

The resulting [H^+]-values were 159.4–160.9 mN, showing only a very small reduction of the acidity.

Thus the lower C_0-values in man, Table 2.I (compared with C_0 in the dogs) are not explained by "instillation in the pyloric part". As at least some of the gastric secretion in the dog experiments must be expected to flow over the pyloric part (where back diffusion should also take place) these calculated "instillations" in man would scarcely give even these theoretical differences due to the experimental conditions. Consequently *the C_0-differences between man and dog have to be taken for the present as experimental realities.*

Comparison of k-values for secretion and instillation experiments

As the role of the back diffusion of H^+-ions from an acid secreting stomach back to the circulation has been a matter of much discussion a series of experiments with intragastric instillation of HCl were made to determine if the back diffusion (expressed by the permeability coefficient, k) could account for the decrease in the acidity after the instillation. In one subject (B. I.) instillations of about 30–40 ml of HCl (154–119 mN) were made. In each case the stomach was emptied as completely as possible ten minutes after the introduction of the

acid. To check that there was no fluid loss into the duodenum phenolred (estimated by the absorbance at the isobestic point, 465 mμ) was added to the instilled solution. Penner, Hollander and Saltzman (1938), Hollander and Penner (1940), Penner, Hollander and Post (1940) and Öbrink (1948) have used phenolred for this purpose.

The calculation of k from Eq. 2.6 in man is, however, complicated by the basal secretion which is always present. In a resting stomach the acidity of instilled HCl always approaches zero, where as in a secreting stomach the final acidity will be determined by the secretion rate. Öbrink (1963) calculated the time course of the acidity in such an instillation experiment as

$$H = \frac{C_0}{1+\frac{k}{v}}\left(1 - \frac{1-\frac{H_0}{C_0}\left(1+\frac{k}{v}\right)}{\left(1+\frac{vt}{p}\right)^{(1+\frac{k}{v})}}\right). \qquad (2.8)$$

As the values of C_0 and v (basal secretion) were known, k could be solved from Eq. 2.8. Most experiments had to be excluded because of extragastric dilution and loss of acid into the duodenum, but from five experiments a mean value of $k = 0.43$ was obtained.

The mean k-value obtained from *secretion experiments* without instillation of acid was 0.36 (from both Eqs. 2.1 and 2.2). Both values are certainly liable to errors due to experimental uncertainties. They are, however, of the same order which seems to support the view that the acidity decrease can be explained on a basis of back diffusion.

Introduction of glycine to determine C_0

To estimate the primary acidity (C_0) at secretion rates other than the maximal ones a glycine buffer (0.25–0.33 N) was used as according to Teorell (1940). Glycine results in an increase in the pH of the gastric contents and thus in a smaller concentration gradient which should reduce the back diffusion possibly to an insignificant level. As mentioned above indirect estimates of C_0 in intact stomachs must be considered a little uncertain, since it is not possible to tie off the cardia and pylorus. Uranine was injected intravenously before the instillations (see page 15) to detect whether duodenal regurgitation occurred. With this precaution 30–50 ml of glycine was instilled into the stomach of one of the dogs (L.) during histamine induced steady

gastric secretion. The H^+-ion concentration gradient was calculated to be diminished about 60–120 times by the glycine. The gastric contents were removed about ten minutes after instillation. The volume increment was calculated directly both from the difference between volume removed and volume instilled and also by determination of the final glycine concentration after a formal titration according to Sørensen (1908). The latter procedure also gives a check of the total recovery of the glycine (cf. Linde, Teorell and Öbrink, 1947). Most experiments were spoiled by extragastric dilution and losses of glycine. C_0 could be calculated from four experiments and a mean value of 163.5 mN was obtained. This value agreed rather well with the mean value of 161.6 from the secretion experiments in the same dog (calculated from the Eqs. 2.1 and 2.2). On account of the experimental difficulties the instillation experiments were considered not suitable for human subjects.

Comments

The rather good fit of both Eq. 2.1 and Eq. 2.2 with the experimental data justifies the calculation of C_0 by either of these equations. In Table 2.I it can be seen that the sum of the least squares, $\Sigma\, d^2$, is numerically smaller when using Eq. 2.2 than with Eq. 2.1 (except for H. C.). This should mean that the values of C_0 and k obtained from Eq. 2.2 should be more representative. All dogs gave higher values than the highest C_0 of the human subjects (Table 2.I).

This demonstrates that the primary acidity in man is lower than in the dog. There seemed to be a tendency for the human primary acidity to be higher with increasing age, but the material is rather too small for the significance of this to be assessed.

The secondary acidity $[H^+]$ in Eq. 2.1 and Eq. 2.2 according to the "diffusion theory" is dependent on the magnitude of the permeability coefficient, k. This means for any given value of the primary acidity the k-value and secondary acidity vary inversely. In Table 2.I the highest acidity measured in any experiment for each human subject and dog is given. The lowest of the highest $[H^+]$ values measured in the dogs was 12 mN greater than the highest value in the human subjects.

If the k-values were found to be of a similar magnitude it should be valid to compare the acidity, for any particular secretion rate, v

(for instance $v = 2.5$ ml/min), between man and dog. In Table 2.I it is shown that this comparison indicates a higher acidity in the dog.

The highest acidity values reported in man are in mN, 140 Flensborg (1944), 140 Hanson, Grossman and Ivy (1948), 149 Nordgren (1958), 150 Kaijser (1943), 150 Hirschowitz (1961), 152.8 Ihre (1938) and 154 Welin and Frisk (1936).

In dogs the highest acidity values observed are 155 Hanson, Grossman and Ivy (1948), 158 Marks, Komarov and Shay (1958), 160 Thull and Rehm (1956), 160 Marks, Komarov and Shay (1960) and 161 Öbrink (1948). For comparison, acidities of 167 Gudiksen (1950) and about 170 Linde (1950) have been found in cats. It thus seems:

(1) *That the primary acidity in man is lower than in dog and*
(2) *That the acidity regulation is qualitatively the same for both man and dog and the "diffusion theory" fits in with the relationship observed between acidity and secretion rate.*

The observation that man and dog have different primary acidities is important, because it follows that man and dog should have a different ion composition of the "primary juice" and this will be discussed in a later part of this investigation.

The permeability coefficient, k

As the sum of the least squares ($\Sigma\, d^2$, see Table 2.I) is smaller when using Eq. 2.2 than Eq. 2.1 (except for subject H. C.) the k-values (like the C_0-values) calculated from Eq. 2.2 can be considered more representative. Nordgren (1958) in man claimed to have found a relationship between the permeability coefficient, k, and the maximal secretion rate, although the correlation was not very high. In this material when k was plotted against the maximal secretion rate, a_1 (see previous chapter), no certain correlation was found, but this may be due, however, to the rather small number of subjects who were studied.

It is evident that at submaximal gastric secretion rates a low k-value will yield a higher acidity (i.e. the secondary acidity) than will a high k-value (the primary acidity is assumed to be invariant). A

subject with a low k-value thus could be said to have a *hyperacidity* while a subject with a high k-value would be *hypoacid*.

If only the acid output is measured the terms hypersecretion (see previous chapter) and hyperacidity are more difficult to interpret. Hyper- and hypoacidity are thus defined in terms of the acidity at a certain secretion rate. It can be estimated from the k-value (see Eq. 2.1 and Eq. 2.2).

CHAPTER 3

The Relation between the Chloride Concentration and Rate of Gastric Secretion

Chloride is the predominant anion and is a satisfactory index of the sum of cations in the gastric secretion.

The concentration of the hydrogen ion is always less than that of chloride, the excess of which is often referred to as neutral chloride.

The chloride concentrations (both total and neutral) have been related to other parameters of the gastric secretion (e.g. the acidity and the secretion rate). *Recti*linear relationships have been claimed between:

(1) total chlorides and acidity, in pouch dogs Hollander (1932), Gray, Bucher and Harman (1941).

(2) neutral chlorides and acidity, Hollander (1932), Gray, Bucher and Harman (1941) in dogs and Fisher and Hunt (1950) in man using Ihre's data (1938). Through extrapolation to $[H^+]=0$ the neutral chlorides were calculated as 130–140 mN. Ihre (1938) in man, however, taking in account back diffusion concluded that there was a curvilinear relation between total chlorides and acidity.

Teorell (1933, 1939, 1947) found that for chloride the results of model experiments and instillation experiments on cats were in agreement with the predictions of his diffusion theory, i.e. the relationship between total chloride and acidity was *curvi*linear. He also confirmed the existence of the predicted temporary "dip" in the chloride concentration in instillation experiments. Gray, Bucher and Harman (1941) concluded there was a hyperbolic relation between secretion rate and total chloride concentration. They, however, had no analytical data at the very low secretion rates, under which conditions in pouch dogs Öbrink (1948) and Linde and Öbrink (1950) did not find any great $[Cl^-]$ decrease, and concluded that these results supported the diffusion theory. A rectilinear correlation between the chloride output and the secretion rate was found by Gray, Bucher and Harman (1941).

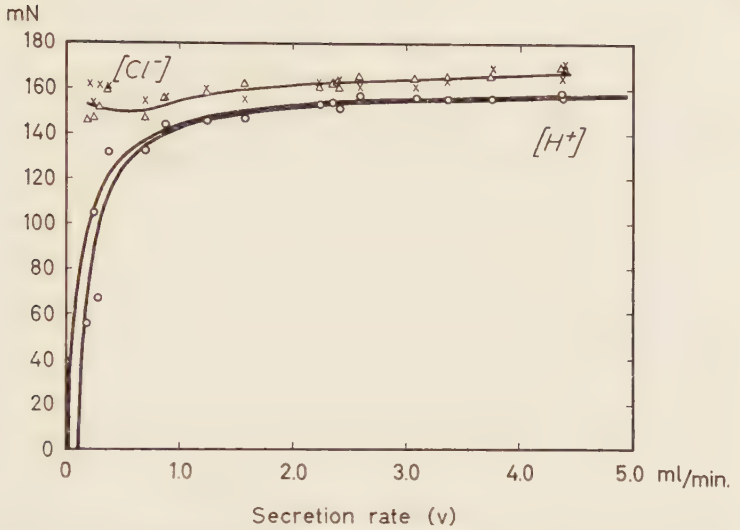

Fig. 3.1. The variation of $[Cl^-]$ in gastric secretion at different steady rates. (Dog M.) The acidity curves are the same as in Fig. 2.1. $[Cl^-]$ is represented by unfilled triangles. The crosses represent the sum of $[H^+]$, $[K^+]$ and $[Na^+]$. The chloride curve was drawn by eye.

Although the chloride concentration and output thus have been correlated with secretion rate in pouch dogs, the situation in the intact stomach of dogs and man has not been investigated extensively and it was considered of interest to study further this problem.

Results

Figs. 1.1 and 1.3 show the variations of the chloride concentration in typical experiments. The steady state values of $[Cl^-]$ and $[H^+]$ were plotted against the corresponding secretion rates in Fig. 3.1 (dog M) and Fig. 3.2 (subject K. G. K.). It can be seen that $[Cl^-]$ (open triangles) approximately equals the sum of $[K^+] + [Na^+] + [H^+]$ (crosses). No attempt was made to fit a regression equation to the chloride values since they appear to represent the sum of all the cations.

The net output of Cl^-, vCl, is therefore also a measure of the net output of the cations. In Fig. 3.3 Cl^- output is plotted against the secretion rate, v. As can be seen (Fig. 3.3), this is apparently a straight line except for the lowest v-values.

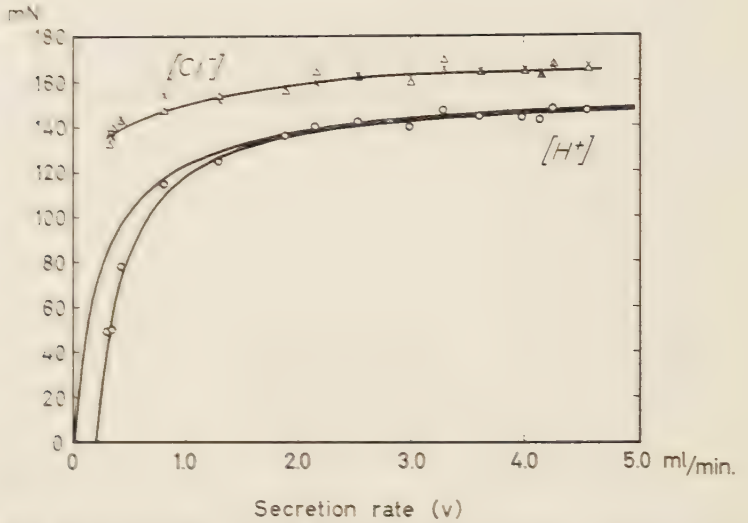

Fig. 3.2. The relationship between the rate of gastric secretion and [Cl⁻] in man. (Subject K. G. K.) The acidity curves are the same as in Fig. 2.2. The notations are is the same as in Fig. 3.1.

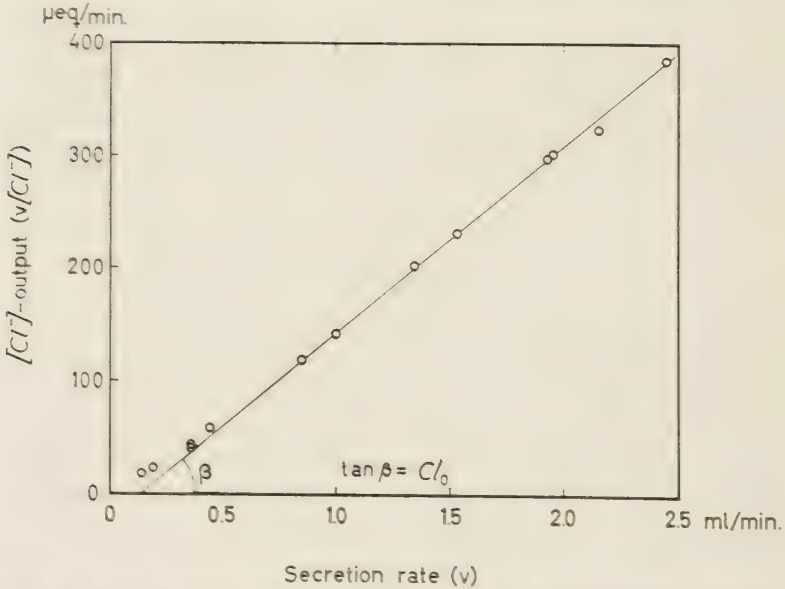

Fig. 3.3. Rate of gastric secretion plotted against output of total chlorides, i.e. $[Cl^-]$ per unit time. The continuous line was drawn by eye through the experimental points. The slope of the continuous line, tan β should equal Cl_0, i.e. the chloride concentration in the "primary secretion" see text. (Subject G. L.)

Discussion

The values of the total chloride concentration in secretion experiments have been found to range between about 140 and 170 (mN) in man (Ihre, 1938) and in pouch dogs about 140–170 (mN) (Öbrink, 1948).

The maximal chloride concentration in man was found to reach a level of about 170–180 (mN) (Hirschowitz 1961). The equilibrium Cl^--concentration as found by instillation experiments at quasi-zero secretion rates tends to the values of about 140–150 (mN) Teorell (1933) or 140 (mN) Kaijser (1943) in cats and in man about 125–135 (mN) Ihre (1938) or 120 (mN) Kaijser (1943). In the present instillation experiments $[Cl^-]$-values of about 140 (mN) were obtained. Difficulties in excluding extragastric admixture in man may explain the variations found. In the present secretion experiments the range for the chloride concentration was in man 119–167 (mN) and in dog 154–176 (mN). Both in this material and in the work cited above there was no significant difference for the upper limit of the total chloride concentration between man and dog.

In order to calculate the primary chloride concentration, Cl_0, i.e. the concentration as the juice emerges from the secretory cell, the output of the Cl^- per minute (vCl) was plotted against the secretion rate, v, Fig. 3.3. As can be seen there is a linear relationship except at the lowest v-values which means that the Cl^--concentration tends to change very little except at very low secretion rates. Hirschowitz (1960) also found linearity between Cl^- output and the gastric osmolar clearance (=the secretion rate times the quotient osmotic pressure of gastric juice/plasma). The straight part of the curve may be considered as an asymptote and its slope would then be a measure of Cl_0 which has been calculated in Table 3.I. There was no obvious difference between man and dog (Table 3.I).

Comparison of $[Cl^-]$ in the "primary secretion" of man and dog

A comparison between the Cl_0-values and the earlier calculated mean values of the primary acidity, C_0, from Eq. 2.1 and Eq. 2.2 (see chapter 2) should give information about the amount of neutral

TABLE 3.I. *Data of the calculation of the total* $[Cl^-]$ *and the neutral* $[Cl^-]$ *in the "primary secretion".*

Subject	Number of Experiments	Cl_0 mN	C_0 (mean from Eqs. 2.1 and 2.2)	$Cl_0 - C_0$ (mean) mN	
K. G. K.	15	183	155.7	27.3	
B. I.	18	175	155.9	19.1	
H. C.	10	166	147.0	19.0	
R. N.	12	158	128.3	29.7	
G. L.	13	165	145.7	19.3	$M = 22.9$
Dog L	8	165	161.6	3.4	
Dog M	17	168	161.6	6.4	$M = 4.9$

chlorides present in the "primary secretion". There seems to be a striking difference between man and dog in this respect; a value of about 20–25 mN was calculated for man and about 5 mN for the dog. It thus appears that man has a lower acidity but a higher neutral chloride concentration in the "primary secretion" compared with the dog.

CHAPTER 4

The Relation between the Sodium Concentration and Rate of Gastric Secretion

At higher rates of gastric secretion the sodium concentration is lower, in contrast to the acidity which is higher. HOLLANDER (1952) showed in pouch dogs an inverse rectilinear relationship between [Na^+] and [H^+]. In man RIDDELL, STRONG and CAMERON (1960) and HIRSCHOWITZ (1961) found that a curvilinear equation fitted their data better. GRAY and BUCHER (1941) in pouch dogs concluded that the [Na^+] was a hyperbolic function of the secretion rate. From his diffusion hypothesis TEORELL (1947) derived the relation,

$$Na = \frac{S_0}{\frac{v}{r} + 1}, \tag{4.1}$$

where Na = the sodium concentration observed (mN),
v = the rate of gastric secretion (ml/min) (in Teorell's notation q),
S_0 = the sodium concentration (mN) when $v = 0$ and
r = the permeability coefficient for Na^+ (ml/min).

In model experiments he found that Eq. 4.1 fitted the experimental data rather well.

LINDE and ÖBRINK (1950) in pouch dogs found Eq. 4.1 fitted their results in secretion experiments. The purpose of this study was to relate [Na^+] with the secretion rate in intact stomachs of man and dog.

Results

The relationship between sodium concentration and acidity and secretion rate during steady state conditions with continuous histamine stimulation is illustrated in the dog in Fig. 1.1 and man in Fig. 1.3. The different steady state values of [Na^+] and [H^+] from each single experiment are plotted against the corresponding rates of gas-

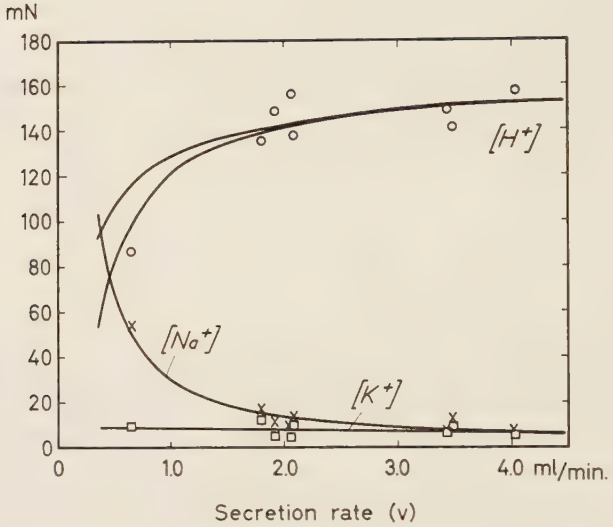

Fig. 4.1. The relationship between the rate of gastric secretion and $[Na^+]$ and $[K^+]$ during steady state conditions. The extrapolation to $v = 0$ was considered uncertain, because of the few experimental values at low rates of secretion. The regression curve for $[Na^+]$ (marked with crosses) was obtained from Eq. 4.1. The $[K^+]$-secretion rate relationship (unfilled squares) is represented by a straight line. (Dog L.)

tric secretion in the same subject, Fig. 4.1 (dog L) and Fig. 4.2 (man G. L.). The inverse relation between $[Na^+]$ and $[H^+]$ is obvious.

The scattering of the results is bigger at lower than at higher secretion rates (Fig. 4.2). This may be due to the difficulties in controlling extragastric admixture.

The regression curve for $[Na^+]$ was obtained by using the method of least squares with Eq. 4.1.

Estimation of the parameters in Eq. 4.1

The form of the relationship in Eq. 4.1 is of such a kind that a direct regression analysis on the basis of least squares principle will involve certain difficulties. If instead the logarithms of both sides are taken a linear relationship is obtained between the variables log Na and log $(v - r)$

$$\log \mathrm{Na} = \log rS_0 - \log (v + r). \tag{4.2}$$

The estimation of the parameters can be performed in the following steps on the basis of the above equation:

(1) Let the parameter r have a plausible *a priori* value.
(2) Estimate log rS_0 according to the L.S. principle.
(3) Calculate the sum of the squared residuals.

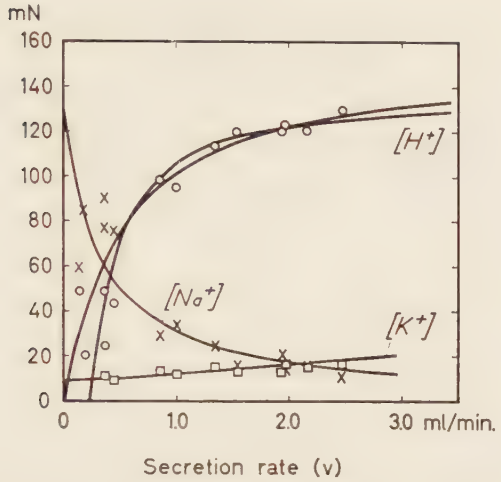

Fig. 4.2. The same relations as in Fig. 4.1. (Subject G. L.)

(4) If the above steps have been made for several values of r it is possible to plot the sum of the squared residuals against the r-values and thus find graphically that value of r which makes the sum of the squared residuals a minimum.

The regression curves for the acidity were derived from Eq. 2.1 (the curve passing through the origin) and Eq. 2.2.

The curves obtained from man and gastric fistula dogs were in general similar.

Discussion

Eq. 4.1 is a hyperbolic function with an asymptote ($r = -v$) parallel with the y-axis. A small error in r means a small displacement of the asymptote along the x-axis which would result in a rather large error in the value of S_0. When applying the method of least squares it is sometimes possible to get negative S_0-values. This is especially likely to occur in subjects with sparse data from experiments with low secretion rates (Table 4.I). A trial was made therefore to estimate S_0 in another way. Log [Na^+] was plotted against v for the whole material and extrapolated to $v = 0$ (Table 4.I). In those cases where S_0 could be calculated from the hyperbolic Eq. 4.1 a check on the validity of this second procedure was obtained. The agreement was acceptable.

In the acidity secretion rate relation the acidity curve appeared to

TABLE 4.I. *Calculated data from the relationship between rate of gastric secretion and [Na^+].*

Subject	Number of experiments	r ml/min	S_0 mN	S_0 graphically mN
K. G. K.	15	−0.1	−166.5	120
B. I.	18	−0.4	−39.8	135
H. C.	10	0.4	113.5	96
R. N.	12	1.1	84.9	85
G. L.	13	0.3	131.9	135
Dog L	8	−0.1	−267.9	87
Dog M	17	−0.1	∞	130

intersect the positive x-axis in some cases (Eq. 2.2). The reason for this may be incomplete mixing of the gastric contents which is not accounted for in Eq. 4.1. If Eq. 2.2 is a satisfactory description of the acidity secretion rate relationship then physically impossible values of r (negative) and S_0 (tending to infinity) may result if Eq. 4.1 is used to analyse the [Na^+] results.

The range for the [Na^+] values was 90.1 to 2.9 (mN) in man and 82.5 to 2.5 (mN) in dog, i.e. there was a great similarity between the species. Furthermore the decline in [Na^+] with increasing secretion rates (Fig. 4.2) together with the small sodium concentration found at the higher secretion rates supports the diffusion theory and the results do not contradict the idea that [Na^+]$\rightarrow$0 when v becomes very large (i.e. that the "primary secretion" contains no sodium).

CHAPTER 5

The Relation between the Potassium Concentration and Rate of Gastric Secretion

Gastric secretion always contains alkali ions and at low secretion rates sodium predominates. At higher secretion rates sodium diminishes progressively being largely replaced by H^+-ions and the greater part of the alkali ions then consist of potassium. If it is assumed that the "primary secretion" does not contain any Na^+ the increase in $[Na^+]$ with decreasing secretion rate can be explained entirely by diffusion of Na^+ through the stomach wall. As potassium, however, does not decrease (but instead at least in man increases) with increasing secretion rate, the relation between secretion rate and potassium similarily cannot be explained in the same way as for sodium. It seems likely that potassium also is secreted in the "primary secretion" (cf. Linde and Öbrink, 1950) in contrast to sodium.

The relations between $[K^+]$ and $[H^+]$ and between $[K^+]$ and secretion rate

Correlations between the potassium concentration and the acidity or the rate of gastric secretion have been claimed by several authors, and these relationships have been a matter of much discussion. After a single subcutaneous injection of histamine Saemundsson (1948), Werther, Parker and Hollander (1960) in man and Hollander (1952) and Hollander and Colcher (1960) in pouch dogs (the last named also gave repeated subcutaneous injections of histamine) did not find any constant relationship between $[K^+]$ and $[H^+]$ or $[K^+]$ and secretion rate. On the other hand a definite correlation between $[K^+]$ and $[H^+]$ was found in human subjects who had received a single subcutaneous injection of histamine (Riddell, Strong and Cameron, 1960) and in cats after continuous intravenous injection of histamine (Blair, Harper, Harris, Reed and Wilkinson, 1960; and Blair, Harper and Yassin, 1961). Further Riddell, Strong and Cameron

(1960) found a positive linear relationship between $[K^+]$ and rate of gastric secretion in man. In pouch dogs Gray and Bucher (1941) after repeated subcutaneous injections of histamine and Linde and Öbrink (1950) after continuous intravenous injection of histamine got a fairly constant $[K^+]$ at varying secretion rates.

Hirschowitz (1961) found that the relationship between K^+ and H^+ was disturbed by atropine or $NaHCO_3$. After parenteral administration of atropine or $NaHCO_3$ in man during histamine stimulation there was a fall in $[K^+]$ while $[H^+]$ remained unchanged. The effect of $NaHCO_3$ cannot be fully evaluated as the acid-base status was incompletely analyzed.

In conclusion it may therefore be said that there is thus much evidence of a correlation between $[K^+]$ and secretion rate both with and without steady state conditions, but on the other hand there has been objection to the existence of such a correlation.

The situation is therefore somewhat confused and more information about the potassium concentration in gastric secretion is desired. Furthermore in view of a possible connection with the "primary secretion" of acid and the difference between the primary acidity of man and dog (chapter 2), potassium deserves close attention. It is here relevant to recall that potassium has been considered to be secreted along with the hydrogen ions in the "primary secretion" (Heinz and Öbrink, 1954).

To obtain more information and comparable experimental conditions a method giving steady state conditions is preferable and was therefore used in this study in both man and in intact stomachs of dogs. As discussed in an earlier chapter only repeated subcutaneous injections or continuous intravenous injections (but not a single subcutaneous injection) of histamine can give steady state conditions.

Results

Fig. 1.1 (dog) and Fig. 1.3 (man) illustrate experiments with continuous intravenous injection of histamine. During a steady state in the rate of gastric secretion the potassium concentration remained fairly constant. The relationship between secretion rate and $[K^+]$ is shown in Fig. 4.1 in dog and Fig. 4.2 in man. The experimental points fitted well to a straight line. The range of the steady state

TABLE 5.I. *Data obtained from the [K⁺]-secretion rate relationship.*

Subject	n	[K⁺] for $v = 0$ mN	$\frac{d[K^+]}{dv}$ mN · $\frac{min}{ml}$	[K⁺] for $v = 4$ mN	Cl_0–C_0 mN	[K⁺] in gastric secretion, range mN
K. G. K.	15	8.7	1.74	15.7	27.3	7.9–16.9
B. I.	18	7.3	3.28	20.4	19.1	8.8–19.3
H. C.	9	11.6	2.19	20.4	19.0	11.1–18.9
R. N.	10	7.9	2.79	19.1	29.7	9.3–18.6
G. L.	10	8.1	4.19	24.9	19.3	11.2–19.1
Dog L	8	9.4	−1.59	6.2	3.4	5.0–11.8
Dog M	16	5.9	−0.35	5.2	6.4	3.7–8.1

values of [K⁺] in the gastric secretion for each subject is given in Table 5.I. The variation of [K⁺] in the dog experiments in this material is bigger than LINDE and ÖBRINK (1950) found in pouch dogs where, however, the experimental conditions as regards extragastric admixture must be more favourable.

The [K⁺] during steady secretion rate in the present dog experiments tended to decrease slightly with higher rates of gastric secretion. This was in contrast to man, where [K⁺] was always greater with higher secretion rates.

Because the volumes of the gastric juice were sometimes too small [K⁺] could not be determined in these samples with sufficient accuracy.

Discussion

Calculation of the regression line

Starting with the assumption that potassium is secreted by the parietal cells and that the mucosa is permeable to it HEINZ and ÖBRINK (1954) derived an equation which indicated that there should be a curvilinear relationship between secretion rate and [K⁺]. The equation was applied to this material but it is rather laborious to use. The analysis showed that within the range of secretion rates used the curvilinearity was insignificant and in this case an approximately straight line was obtained. An equally good fit for the relation be-

tween $[K^+]$ and secretion rate was obtained with the linear regression line calculated by the method of least squares. In Table 5.I the values for the y-axis intercept (i.e. $[K^+]$ for $v=0$), and the slope of the straight line, here denoted as $d[K^+]/dv$, are given. As can be seen (Fig. 4.1 and Fig. 4.2) $[K^+]$ shows a good correlation with the rate of gastric secretion using a rectilinear relationship.

Magnitude of $[K^+]$ in the "primary secretion"

Since a curvilinear relationship with a maximal $[K^+]$-value was not calculated for the relationship between $[K^+]$ and the secretion rate the $[K^+]$-value corresponding to the infinitely high secretion rate cannot be calculated from the straight regression line. To estimate the $[K^+]$ in the "primary secretion", the values of $[K^+]$ corresponding to a secretion rate of 4.0 ml/min are given in Table 5.I. The value of 4.0 ml/min was chosen as an estimate of the maximal secretion rate, it being an approximation of the mean of the a_1-values (see chapter 1). A comparison with the neutral chloride concentration calculated in the "primary secretion" (see chapter 3) is given in Table 5.I and shows that the higher $[K^+]$ in man can account for the higher neutral chloride concentration and the lower primary acidity in man compared with the dog.

It was shown in chapter 3 that the primary chloride concentration was not different in man and dog. Chloride is practically the only anion in the gastric secretion which therefore is equiosmolar in dog and man. The higher $[K^+]$ in man could thus not be accounted for by a higher osmolarity in the "primary secretion". This supports the rather essential conclusion that *the "primary secretion" in man* though of the same osmolarity has a different composition from that of the dog having *a higher* $[K^+]$ *and a correspondingly lower primary acidity.*

The origin of K^+ in the gastric secretion

The potassium concentrations calculated for $v=0$ (i.e. at secretory arrest) in man and dog were not significantly different (Table 5.I). This is of some interest, because it suggests that at secretory arrest potassium tends to reach the same concentration in both man and dog. It seems possible that at secretory arrest the intragastric $[K^+]$ is in a steady state between the surrounding "compartments" i.e. between the intracellular and the plasma potassium.

The plasma potassium concentration in dogs (Prosser, 1950) is not very different from that in man (Nadler, 1953, Bernstein, 1954). If the intragastric potassium (secretory arrest) is considered as being in a compartment lying in contact with both the intracellular and extracellular (plasma) spaces the similarity of the *intragastric* and *extra*cellular (plasma potassium) concentrations in man and dog might perhaps mean that the *intra*cellular [K^+]-values are similar in man and dog.

The parietal cells are only part of the total cell population of the mucosa. This means that [K^+] in the parietal cells is not necessarily the same as the average for the whole cell population. In fact, Davenport and Alzamora (1962) found differencies in [K^+] between parietal cells and the surface epithelial cells in the frog gastric mucosa. It is therefore possible that, although a rather similar average [K^+] in the whole cell population in man and dog is likely (see discussion above), the [K^+]-values for the parietal cells may be different in dog and man. As potassium probably to a large extent is derived from the parietal cells (see chapter 7) such a difference in the two species may cause different concentration of K^+ in the "primary juice". In fact, at higher rates of gastric secretion the difference in [K^+] is manifest.

Another explanation for the difference of the primary K^+-concentration might be different "rate constants" for the secretion of K^+ from the parietal cells. In such a case we do not need to assume different intracellular concentrations in the parietal cells of man and dog. Such differences in "rate constants" are not unlikely as was shown by Burgen (1956) to occur in salivary glands when the degree of stimulation changed.

In short the study supports the view that the "primary secretion" contains potassium and in a higher concentration in man than in dog. This [K^+] is dependent on the secretion process. Further [K^+] in the stomach contents at secretory arrest is not different between the species. The findings are good reason for further studies of the kinetics of potassium transport in the gastric juice.

CHAPTER 6

The Effect of Histamine on Potassium Concentration in Blood; *in vitro* and *in vivo* Experiments

After continuous intravenous injection of histamine there was a significantly higher output of potassium in the gastric secretion of man than in dog. At secretory arrest [K^+] was calculated to be not significantly different between man and dog (chapter 5).

This study attempts to analyze the mechanisms underlying the higher [K^+] in gastric juice in man during secretion. The aim was to study if the higher gastric potassium concentration obtained in man was a passive process, i.e. due to simple diffusion equilibrium with plasma potassium, caused secondarily by an increase in plasma potassium (from systematic potassium liberation induced by histamine).

As discussed in chapter 5 plasma [K^+] appears to be similar in both species, but this is no measure of the kinetics of potassium exchange. It is quite possible that in man more potassium is liberated from different parts of the body and then transported to the stomach mucosa.

It has been suggested that histamine may act by liberating potassium from tissues. In cats histamine has been shown to increase the plasma potassium concentration (MacMillan, 1956, 1957) and this effect could be antagonised by antihistamines (promethazine or pyrilamine).

Similar results have been reported in rabbits and guinea pigs, (Ambrus and Ambrus, 1952). Liberation of K^+ from tissues after histamine administration was found by Parrot, Thouvenot and Longuevalle (1952, 1953), for example, on guinea pig intestine, in cat red blood cells (MacMillan and Vane, 1956) and in cat striated muscle (MacMillan, 1955).

It has been shown in isolated frog gastric mucosa during secretion that an increase of [K^+] in the nutrition fluid gave an increase in the net transport of K^+ to the secretory side (Harris, Frank and Edelman, 1958). With the [K^+] on the secretory side 4.0 mN/l higher

than on the "blood" side there was still a moderately reduced net transport across to the secretory side.

It seems justified therefore to consider whether the higher K^+-output in gastric secretion in man depends on a higher extragastric K-liberation than in dog. At this point it should be mentioned that $[K^+]$ in red blood cells of the dog was found to be 10 mN Bernstein (1954), 9 mN Ponder (1948) and 8.7 mN Kerr (1937) compared with the much higher values in man e.g. 106 mN Bernstein (1954), 100 mN Ponder (1948) and 99.2 mN Lans, Stein Jr. and Meyer (1952). Thus in marked contrast to the dog there is clearly a not unimportant potential potassium pool in the red cells of man.

In this study both *in vitro* experiments with whole blood and *in vivo* determinations of plasma $[K^+]$ before and during histamine administration were made. The aim of the *in vitro* experiments was to study whether potassium was liberated from the potassium-rich erythrocytes of man (measured as an increase in plasma $[K^+]$) after addition of histamine. The aim of the *in vivo* experiments was to study whether there was any liberation of K^+ from other parts of the body.

Methods

Blood was collected in tubes treated with dimethyldichloresilane (Repelcote®, Hopkins and Williams Ltd) and containing a small amount of heparin. Plasma was obtained by centrifugation. Dilutions were made with 0.1 % ammoniated water to solubilise particulate material as according to Barer and Gaffney (1957). Potassium was determined flamephotometrically. 2 ml of plasma was diluted 1 : 5 with 7 ml ammoniated water and 1 ml 100 mN LiCl. $[K^+]$ in the red blood cells was calculated from the hematocrit and potassium concentrations in whole blood (hemolysed with ammoniated water) and plasma. No correction was made for trapped plasma.

In vitro experiments

Histamine dihydrochloride in differing amounts (see Table 6.I) was added to the blood samples which were then shaken for about 15 minutes together with the controls (without any histamine added) before centrifugation. The blood used was up to 5 days old.

TABLE 6.I. *Experiments (in vitro) in man and dog showing [K^+] in blood plasma without and with histamine addition.*

	Man		Dog	
	Histamine conc. μg/100 ml blood	[K^+] mN	Histamine conc. μg/100 ml blood	[K^+] mN
	0.0	4.3	0.0	6.1
	12.5	4.2	12.5	5.7
	25.0	4.3	25.0	6.1
	67.5	4.3	67.5	5.8
	125.0	4.2	125.0	6.1
In red cells	–	97.8	–	7.1

In vivo experiments

Blood was taken from a peripheral vein before the histamine injection and during a steady gastric secretion rate induced by histamine. In these experiments the antihistamine, chlorpheniramine, was given to the subject as in the other experiments with gastric secretion (see earlier chapters).

In both types of experiments the effect of histamine administration as the plasma [K^+] was compared.

Results

In vitro experiments

In pouch dogs ÖBRINK (1948) found a linear relationship between the rate of continuous intravenous histamine injection and the plasma concentration of histamine. For injection rates, giving an almost maximal rate of gastric secretion, plasma concentrations of 60 μg/100 ml of histamine dihydrochloride were obtained. With 48 μg/100 ml of histamine base in plasma, EMMELIN, KAHLSON and WICKSELL (1941) observed pronounced pharmacological systemic effects on dogs. It was therefore decided to use blood concentrations of histamine dihydrochloride from 12.5 to 125 μg/100 ml in this study. No antihistamine was used. In Table 6.I results from human and canine blood are shown. In all cases histamine controls were of the same blood

sample as the histamine treated cells. The $[K^+]$-difference with and without histamine was calculated. The mean difference including all histamine levels was for man +0.1 mN ($n=9$.t-test; $t=1.51$; $P>0.1$) and for dog −0.1 mN ($n=8$.t-test; $t=1.01$; $P>0.1$). There was no tendency of increase in $[K^+]$ with increasing amounts of histamine.

Thus, in the concentration range of histamine used and in the absence of an antihistamine, an *in vitro* increase of plasma potassium concentration was not detected.

In vivo experiments

The mean difference between plasma $[K^+]$ before and during the histamine stimulation was −0.289 mN ($n=9$.t-test; $t=2.75$ and $0.05>P>0.02$). As in the *in vitro* experiments there was no successive increase in plasma $[K^+]$ with increasing injection rates of histamine. Thus there was no evidence of an increase in plasma $[K^+]$ during histamine stimulation. Further work would be required to show if the apparent decrease had any significance. Table 6.II shows the $[K^+]$-

TABLE 6.II. *Measured values of $[K^+]$ in gastric secretion.*

Subject	Without histamine stimulation	With histamine stimulation
B. I.	8.8	19.4
H. C.	11.1	18.9
R. N.	9.3	18.6
G. L.	11.2	18.1
Dog L		11.8
Dog M		8.1

TABLE 6.III. *Examples of changes in plasma $[K^+]$ and $[K^+]$ in secretion before and during histamine injection.*

Subject	$[K^+]$ in plasma [mN]		$[K^+]$ in gastric secretion (mN)		Injection rate of histamine $\mu g/kg \cdot hour$
	Before histamine injection	During histamine injection	Before histamine injection	During histamine injection	
B. I. (4)	5.0	5.2	7.9	18.7	17.2
B. I. (5)	5.3	5.0	9.1	14.7	2.3

values in the gastric secretion from some experiments in man and dog during histamine stimulation. Table 6.III shows in two experiments in man (B. I.) with the plasma [K^+] and the [K^+] in gastric secretion before and during histamine stimulation.

Discussion

No evidence of an increase in plasma [K^+] was found either in blood treated with histamine *in vitro* or in blood in *in vivo* experiments after histamine administration. As a significant difference between plasma [K^+] in man and dog has not been established, the higher [K^+] in human gastric secretion during histamine stimulation can not be explained by a higher plasma [K^+] which might give secondarily a higher [K^+] in gastric secretion in man.

A higher potassium liberation in man might not be reflected, however, by an increase in plasma [K^+], if, for example, the rate of potassium loss from the blood was also increased pari passu. This might be of importance if the potassium pools in man were of a higher concentration or were more easily liberated by histamine (if [K^+] was not different) than in dog. It may be noted that antihistamines (which have been shown to block partly at least the K^+-liberation, see above) were given before gastric secretion was induced by histamine.

Human red cells have a higher potassium content than in dog. The muscles which constitute the main storage site for K^+ in the body (Fenn, Noonan, Mullins and Haegue, 1941, Forbes, 1955), have similar [K^+]-values in man and dog (cf. for instance Hastings and Eichelberger, 1937, and Eichelberger and Roma, 1949). It seems not unreasonable to expect that if histamine liberates significant amounts of K from red cells that the K escaping from the potassium rich human cells should have been detected in the *in vitro* experiments.

As man and dog have essentially similar K^+-concentrations in the main storage sites (predominantly the muscles) the possibility remains that K might be more easily liberated in man than in dog. It should be mentioned here that at steady rates of gastric secretion the higher [K^+] in man is maintained on a fairly constant level for several hours. It might be expected therefore that during such conditions a higher plasma [K^+] should be found, if there was a correspondence of steady state [K^+]-levels in gastric secretion and plasma.

Although as mentioned above the KCl concentration on the nutrient side was shown to have an effect on K-transport across the frog gastric mucosa, the increase in intragastric [K^+] during secretion in man does not seem to arise from an increase in blood [K^+]. It seems therefore possible that the *difference in intragastric* [K^+] *between man and dog is dependent on a local secretory mechanism in the gastric mucosa.*

CHAPTER 7

The Movement of Radioactive Sodium and Potassium across the Stomach Wall

As has been described previously (chapter 5) it was found that the intragastric potassium concentration during acid secretion is higher in man than in dog. The total intragastric cation concentration in both species was, however, similar and the primary acidity was shown to be correspondingly lower in man than in dog. Thus a general liberation of potassium from the cells of the body as an effect of administered histamine was not likely to be the cause of the differences in intragastric potassium concentration in man and dog. It was suggested that this difference was probably related to the local secretion process in the gastric mucosa and this motivated a study of the pathways for the transport of potassium in the gastric mucosa.

The movements of radioactive potassium and sodium through the gastric mucosa were measured simultaneously so that they could be compared both during secretion and at secretory arrest.

Material

Cats (weight 1.2–4.2 kg) and young dogs (weight 3.4–6.2 kg) were used in acute experiments.

In two experiments with gastric secretion a Heidenhain pouch dog (weight about 20 kg) was used.

Methods

Procedure

Anaesthesia. In the acute experiments on cats and dogs the animals were anaesthetized first with ether in a closed cage. Anaesthesia was then maintained with Nembutal[8] (Abott) 30–50 mg per kg body weight given intravenously or a mixture of chloralose (1 % solution,

60–100 mg/kg body weight)—urethane (10 % solution 1.0–1.5 g/kg body weight) in a few cases. According to Stewart (1950), MacMillan and Vane (1956), barbiturate anesthesia can influence plasma [K^+]. This might explain the variations in plasma [K^+] observed in the present material.

The abdominal wall was opened and the stomach tied off at the cardia and pylorus (the big blood vessels passing the sphincters were left intact). A glass tube was then inserted into the pyloric end of the stomach. The stomach was then emptied completely at intervals varying between about 2 and 10 minutes (see results) via a rubber tube introduced through the glass tube and the volume of the gastric contents withdrawn was estimated in a measuring cylinder.

In the secretion experiments stimulation was induced with continuous intravenous injection of histamine after 8 mg chlorpheniramine (Allergisan®) had been given intravenously in a single dose.

Blood samples (about 1 ml) were taken via a plastic tube (treated with heparin) inserted in a femoral artery. After centrifugation 0.2 ml of plasma was used for determination of the isotope activities. According to MacMillan and Vane (1956) 20 samples of 1.5 ml blood (at intervals of either 2 or 10 minutes) can be withdrawn from anaesthetized cats without any increase in plasma potassium. The blood samples were centrifuged (for about 8 minutes at about 2000 rpm) immediately after they were taken. The plasma was then removed. This was done to diminish the possibility of exchange with the potassium in the red cells.

Analysis

The acidity was titrated with bromthymolblue. For further description of this method and the determination of Cl^-, K^+ and Na^+, see page 7.

Analysis of Na^{24} and K^{42}

Na^{24} and K^{42} were measured simultaneously in a two-channel-gamma-spectrometer. For details of the technique reference may be made to Öbrink and Ulfendahl (1959) and Bill, Öbrink and Ulfendahl (1959). The gamma-ray energy for K^{42} is 1.53 MeV and for Na^{24} 1.37 and 2.76 MeV. The channels were chosen, so that one channel registered practically no K^{42} activity. The error for the determination of Na^{24} is about 1.3 % and for K^{42} about 1.6 % (20,000 cpm of the

isotopes). With lower counting rates the error becomes greater; this is especially the case if there is a pronounced difference between the activities of the isotopes (Danielson and Sjöstrand, 1963).

The stability of the apparatus was controlled by counting standard samples of Na^{24} and K^{42} at least every hour. The amounts of radioactivity used were 50–70 μC Na^{24} and 50–70 μC K^{42}. The total amounts of alkali cations injected into the animals were about 10 μEq of Na and 45 μEq of K.

Results

Three types of experiments were done.

I. A single dose of K^{42} and Na^{24} was given intravenously during histamine stimulation (dose about 0.5–1.0 mg/hour) to study the pattern of the appearance of the isotopes in the stomach during secretion (10 experiments).

II. In two experiments the K^{42} and Na^{24} were given intravenously without histamine stimulation (i.e. during secretory arrest of the stomach) but with sodium and potassium chlorides instilled in the stomach, in concentrations corresponding approximately to the steady state values of the ions at secretory arrest, see Table 7.I, cats *4* and *5* (mean values). This experiment was done to get information of the isotope fluxes without any net transport of water into the stomach.

III. In two experiments the rate of departure from the stomach during secretory arrest was measured by the disappearance after intragastric instillation of the isotopes in a solution of the same type of composition as above, see Table 7.I, cats *3* and *7* (mean values).

I. *The isotopes injected intravenously during gastric secretion*

Fig. 7.1*a* shows the variation of the specific activities (cpm/mEq) (for practical reasons the specific activity was expressed in cpm/mEq here) of the potassium and the sodium in plasma and gastric juice after a single intravenous dose of K^{42} and Na^{24} during continuous intravenous injection of histamine (cat *6*). This means that a constant secretion rate (ml/min) was maintained with a constant $[H^+]$, $[Na^+]$, $[K^+]$ and $[Cl^-]$ during the whole experiment, i.e. the rate of potassium and sodium output is constant. With a single intravenous injection of K^{42} and Na^{24} the specific activity of potassium (and to a lesser extent also of sodium) reached a *peak* about 8 minutes after the

injection. Subsequently the level of the specific K activity declined and then remained at a *lower* level than the specific activity in the plasma. In all experiments the specific activity of sodium also declined until it reached a level similar or a little higher than the specific activity in plasma.

During gastric secretion and after the initial peak of specific activity had passed and a more or less steady level had been attained the quotient between the specific activities of potassium in gastric juice and plasma was found to be 0.33 (mean) in cats (5 animals, 40 determinations) and 0.57 (mean) in dogs (5 animals, 39 determinations). The corresponding values for sodium were 1.13 in cats and 1.07 in dogs. Table 7.I gives the data in more detail.

II. *The tracers injected intravenously during secretory arrest with an approximately isotonic solution of KCl and NaCl instilled into the stomach*

In Fig. 7.2 (cat *4*) the stomach was in secretory arrest and 7 ml solution containing KCl and NaCl were introduced. In Table 7.I data from the experiments are given. In the experiments with a volume instilled in the stomach the variations in $[Na^+]$ and $[K^+]$ were between some samples not negligible. There was, however, no definite trend in these concentration changes. The gastric contents were then withdrawn as completely as possible at intervals of about 10 minutes. A sample (0.2 ml) was then taken before reintroduction of the contents. As in the experiment of Fig. 7.1*a* K^{42} and Na^{24} were injected intravenously in a single dose. A sharp initial rise of specific activity in the instillation volume was not obtained. Compared with the secretion experiments the specific activity of sodium in the instilled solution increased continuously rather slowly and after 90–100 minutes had reached a level of about 20–30 % of the specific activity in the plasma. Only very low specific activities of K were found intragastrically.

III. *The isotopes instilled in the stomach during secretory arrest*

In order to determine the rate of disappearance of K^{42} and Na^{24} from the stomach during secretory arrest, 7 ml of an approximately isotonic solution (containing NaCl and KCl with K^{42} and Na^{24}) were instilled (see Table 7.I and remarks above about concentration changes). Sampling was done as above (II) at about 10 minute intervals for determination of the specific activities of potassium and sodium and

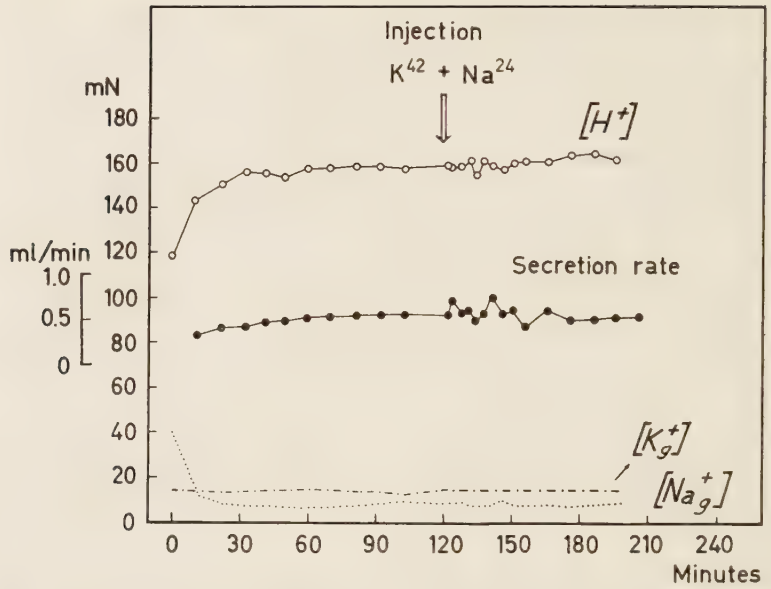

Fig. 7.1 *a*, *b* and *c*. Single intravenous injection of K^{42} and Na^{24} during steady rate gastric secretion (induced with continuous intravenous injection of histamine). (Cat 6.) This figure (7.1 *a*) shows the rate of secretion and $[H^+]$, $[K^+]$ and $[Na^+]$ in the secretion.

flamephotometric analysis. As the fall in specific activity was exponential the logarithm of the specific activity of these ions was plotted against the time thus giving a straight line (Fig. 7.3). From two experiments the mean decrease in specific activity of potassium in the instilled solution was 36 % and for sodium 23 % after 60 minutes. The specific activities in the plasma were always very low, which means that the concentration gradient across the stomach was only determined by the value of the specific activity in the stomach.

Discussion

I. *K^{42} and Na^{24} injected intravenously during gastric secretion*

The peaks of highest specific activity in the stomach contents ocurred about 8 minutes after the intravenous injection of K^{42} and Na^{24}

Fig. 7.1 *b*. The *activities* of K^{42} and Na^{24} (cpm) in plasma and gastric secretion after injection of the isotopes. (Cat 6.)

Fig. 7.1 *c*. The time course of the *specific activities* of K^{42} and Na^{24} in plasma and gastric secretion after injection of the isotopes. (Cat 6.)

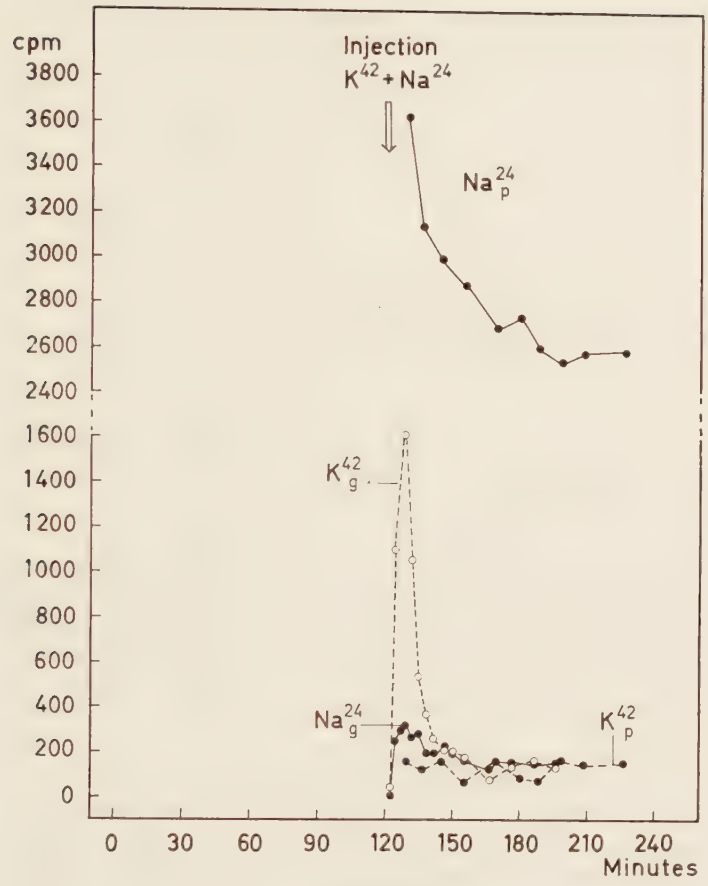

Fig. 7.1 *b*.

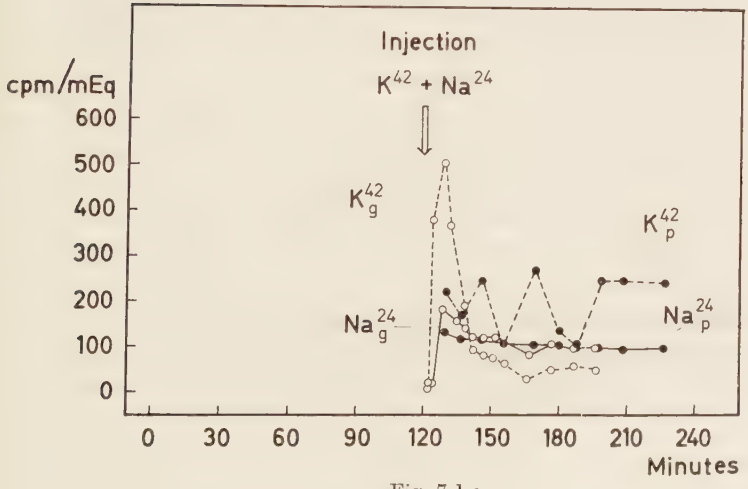

Fig. 7.1 *c*.

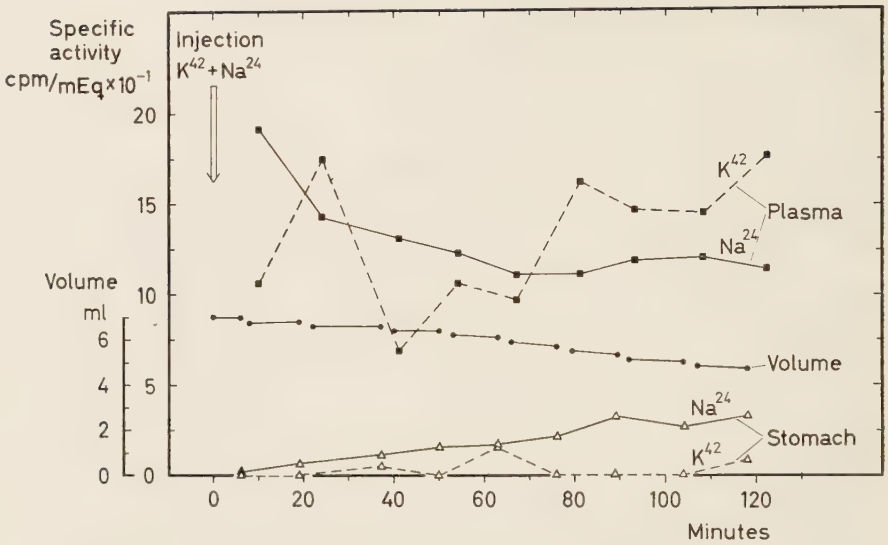

Fig. 7.2. The appearance of Na^{24} and K^{42} in a stomach after a single intravenous injection of K^{42} and Na^{24} during secretory arrest with 7 ml solution (composition, see Table 7.I) instilled in the stomach. Volume in the fig. refers to the intragastric volume. The sharp decline (left as a discontinuity) in volume between each pair of close points is due to the technique: the whole stomach contents were removed, a small sample was withdrawn for analysis and the remainder of the gastric fluid was then replaced in the stomach. (Cat 4.)

(Fig. 7.1*a*). It seems most likely that these peaks reflect, with some time lag, the earlier peaks in the plasma specific activities resulting from the injection of K^{42} and Na^{24}. The width of the peak may be dependent on differences in the transport distance along the crypts. In the solution injected the cpm of K^{42} and Na^{24} were similar. The specific activity of the sodium in the plasma after quasi-complete circulatory mixing therefore became lower than that of potassium because of the much higher plasma sodium concentration. As $[Na^+]$ and $[K^+]$ in the gastric secretion obtained here do not differ very much, this should explain the lower specific activity of sodium in gastric secretion.

The 8 minute interval between the intravenous injection of the isotopes and the peak of specific activity in the gastric secretion should be a measure of the transit time of the tracer from plasma to stomach. The approximatively simultaneous appearance of both sodium and potassium peaks suggest that their transport mechanisms are similar or at least interrelated. Subsequent to the peak value the ratio of the

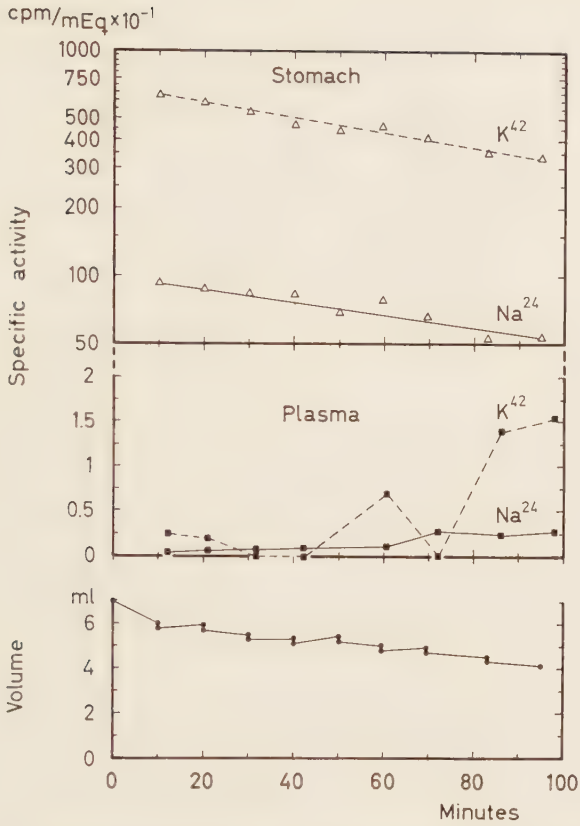

Fig. 7.3. K^{42} and Na^{24} added to a volume (composition, see Table 7.I) instilled in a non-secreting stomach. The steps in the volume-time curve are due to the removal of small volumes for analysis. (Cat 3.) It should be noted that although as in Fig. 7.2, the entire stomach contents were removed and then reintroduced during the sampling that this process has been plotted as though requiring no time. This seems justified because in this experiment the intragastric radioactivity represents the source and thus is withdrawn from the animal periodically.

specific activity of intragastric to plasma potassium falls significantly below unity, while the specific activity of sodium never falls below that of plasma. One explanation for the low potassium value in gastric juice might be that it originates from a compartment of low specific activity.

The intracellular concentration of potassium in the gastric mucosa is much higher than the plasma-$[K^+]$, (Martin, 1955; Davenport and Alzamora, 1962), while the plasma concentration is higher than in-

TABLE 7.I. *Mean values of plasma and stomach contents from the studies of radioactive potassium and sodium movements across the stomach mucosa. The mean values represent 5–14 individual samples, usually 10–14.*

Cats 3 and 7 were experiments with the isotopes instilled in the non-secreting stomach. *Cats 4 and 5* were experiments with intravenous injection of the isotopes and the stomach in secretory arrest. In the other experiments the isotopes were injected intravenously during gastric secretion.

Experiment	Rate of gastric secretion ml/min	Acidity mN	Plasma mN		Gastric contents mN		Plasma cpm		Gastric contents cpm		Quotient of specific activity of	
											Potassium gastric secretion / plasma	Sodium gastric secretion / plasma
			Na^+	K^+	Na^+	K^+	Na^{24}	K^{42}	Na^{24}	K^{42}		
Cat 2	0.37	138	145	4.3	13.8	16.9	2438	238	361	437	0.51	1.36
Cat 6	0.56	159	132	3.3	7.9	14.3	2796	130	171	190	0.29	0.94
Cat 8	0.44	158	154	2.7	11.8	12.7	355	24	31	21	0.21	1.18
Cat 10	0.36	159	158	2.6	12.9	10.6	2237	653	207	486	0.21	1.12
Cat 12	0.22	136	156	3.1	33.3	11.4	3261	342	656	406	0.44	1.05
Dog "Lotta" I	0.15	131	142	4.4	25.7	4.9	1324	74	191	54	0.58	0.88
Dog "Lotta" II	0.26	146	148	3.6	8.2	3.7	800	105	46	42	0.41	1.20
Dog 1	0.19	102	154	4.4	40.4	3.4	2221	649	622	412	0.67	1.07
Dog 2	0.34	136	146	2.8	12.0	2.5	1495	216	128	138	0.77	0.99
Dog 3	0.31	133	150	2.9	13.2	2.8	1328	155	121	103	0.74	1.06
Cat 3			152	3.8	113.7	10.0						
Cat 4			149	3.3	115.1	8.2						
Cat 5			148	3.2	144.2	7.4						
Cat 7			136	4.5	120.6	9.4						

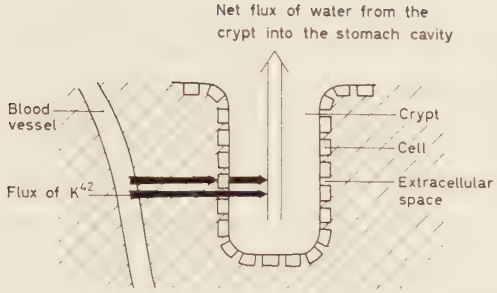

Fig. 7.4. Proposed scheme for the transport of K^{42} from plasma to the stomach cavity during gastric secretion.

tracellular concentration of Na (Ingraham and Visscher, 1939; Davenport and Alzamora, 1962). Thus there is a comparatively large amount of intracellular potassium available which can serve as a diluent for any K^{42} influx. A low (compared with plasma) intracellular specific activity might therefore be expected for potassium. Secretion of this intracellular potassium into the stomach cavity should therefore give a specific activity in the gastric secretion much lower than that in plasma.

To explain the initial peak and the subsequent reduction in the specific activity to a value lower than of plasma, it is proposed that duality of the K^{42} pathway exists, i.e. some K^{42} reaches the crypt lumen by a route which does not involve its dilution with the large intracellular pool of K^{39}. This pathway might be for example extracellular or via an intracellular compartment with a low potassium content (Fig. 7.4).

Assuming an extracellular pathway the peak of specific activity in the gastric secretion would then be the result of the K^{42} not transported through the parietal cells. The experiments were done during steady state gastric secretion. The K entering the stomach by the non-parietal cell pathway would therefore be continually diluted by a "low K^{42}" fluid originating from the parietal cells (low intracellular specific activity). Thus the specific activity of K in the gastric juice would always be lower than that of the plasma. However, the time required for the transport of K into the stomach would delay the appearance of the K peak into the gastric juice and the fact that the specific activity in the stomach is at its peak period higher than that of plasma may be merely a consequence of this time lag.

The specific activity of sodium in the gastric contents never fell below that of plasma. It must therefore be concluded that unlike K^{42} the Na^{24} in its passage into the crypt lumen does not become diluted by the addition of its non-radioactive-isotope. Thus the sodium pattern is consistent with a simpler, e.g. a unicompartmental system such as diffusion through the mucosa. The intracellular sodium content is much lower than that of potassium and the intracellular compartment is thus a much smaller "dilution pool" for Na^{24} than for K^{42}. The specific activity of sodium emerging from a cell will therefore be much nearer the plasma level than in the case of potassium.

After the peak period the specific activity of sodium in the gastric secretion did not fall lower than that in plasma.

II. *K^{42} and Na^{24} injected intravenously and with an isotonic Na/K solution instilled into the non-secreting stomach*

When comparing the results with the different experimental conditions the question arises as to wether other models fitting the experimental data can be proposed. What here has been called diffusion might be influenced by parameters which are difficult to measure such as non-acid components. It is also quite possible that other factors exert some influence on the movements of the radioactive tracers through the stomach mucosa. The electrical potential (i.e. the forces manifested as the electrical potential) might be different (although this difference is not very big) during secretion and secretory arrest. Here a change in electrical potential in the mucosa should, however, influence sodium and potassium in the same direction and is thus unlikely to account for the result obtained. A result here worthy of note is that sodium enters the instilled volume less slowly than potassium during secretory arrest (Fig. 7.2), although the ionic mobility of potassium is greater. The non secretory conditions do not differ from those at secretion only by virtue of the absence of the water secretion. In secretion there is also secretion of H^+ and Cl^-. A low pH of the crypts for instance may profoundly affect the permeability properties of the crypt walls. Other local conditions resulting from secretion such as changed potential differences across the parietal cell membranes may also be important as regards K (or Na) movements. In addition it must be noted that the functional vascular pattern is also much affected in the secretory state. During secretion

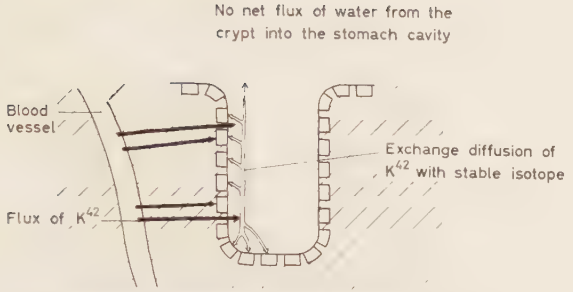

Fig. 7.5. Proposed scheme for the transport of K^{42} from plasma to the stomach cavity during secretory arrest.

the blood flow in the mucosa is increased and thus larger amounts of radioactive plasma pass by.

In these experiments the volume in the stomach was not renewed at the sampling times; after removal of a 0.2 ml sample for the analyses the rest of the gastric contents were returned to the stomach. Thus a peak, such as was found in the secretion experiments (where the stomach was emptied completly at each sampling) would be manifest as a region of much greater slope in the graph relating the specific activity to time. In addition the intragastric volume was rather large and in these cases there was a rather large dilution of any isotope entering which would have the effect of making the determination of such a "peak" in sodium output more difficult. The K output was, in any case so low as to be barely significant.

The low K^{42} output seems likely to be due to the large intracellular dilution space available to it. (Fig. 7.5).

The importance of the crypts for the ion exchange. Except for part of the mucus the gastric secretion originates from the crypts in the stomach wall. In cats these crypts are about 1 mm in length (Toldt, 1881). The distance between the extracellular space and the crypt lumen is of the order 10–50 μ (Johnson, 1910). According to Toldt (1881) there are about 75 crypts per mm^2 of the stomach mucosa. The average diameter of the crypts (after histological treatment in which shrinking occurs which must give an underestimate) was about 0.05 mm (Toldt, 1881). These figures yield a very approximate value of about 12 mm^2 of internal crypt area per mm^2 of surface area tangential to the stomach cavity. This calculation suggests that by far the biggest area for diffusion is in the crypts which would thus be expected to constitute

the predominant transport route from both the extracellular and the intracellular spaces to the stomach cavity.

During secretion the ions can be transported through the crypts into the stomach cavity with the water flux. In the absence of secretion transport from crypt to stomach cavity can occur only by diffusion if there is no mechanical stirring or squeezing.

Heinz (1951), in an attempt to prove the validity of the glycine-instillation method for determining the primary acidity, calculated that in a resting stomach glycine diffusion along a crypt 30 μ in diameter and 300 μ long should be 90 % complete in 1½ minutes. This calculation applied however only to the outer wider part of the crypt and the real diffusion time should therefore be somewhat greater. It however seems likely that the time required for diffusion of K^{42} and Na^{24} into the crypts from the stomach cavity is not the rate limiting step as regards their disappearance after instillation.

As it takes less than 8 minutes for the tracer peak to appear in the gastric contents during steady state secretion, isotope transport from the plasma to the crypts must take not more than 8 minutes.

In the instillation experiments at secretory arrest with the isotopes given intravenously, K^{42} output into the stomach was very slow while there was a much greater and steady increase of Na^{24} (Fig. 7.2).

Regarding the sodium the plasma specific activity is that after the Na^{24} has already been diluted with a large sodium pool in plasma, and in the extracellular or intracellular spaces there is a relatively much smaller diluting pool for Na than for K. Hence it is not unexpected that the Na^{24} activity in stomach is much higher compared with the plasma level than in the case of K. This should also mean that the actual K^{42} output to the stomach should be less.

This fact that sodium increases less slowly than potassium in the instilled intragastric solution may involve other factors. It has been found also that sodium apparently moves faster than potassium in other biological tissues. Thus, for instance, Tasaki, Teorell and Spyropoulus (1961) showed that intracellularly injected Na^{24} passed squid axon membranes faster than K^{42}.

An active process such as expulsion of sodium from the intracellular space as proposed by Ussing (see for instance Ussing *et al.* 1960) could be utilized to explain a smaller distribution volume in the gastric mucosa for sodium compared with potassium. The net effect, with such a system, on K^{42} and Na^{24} passing through the mucosa

would be that potassium would be retained more than sodium similarily as for instance in gel filtration with apparently different distribution volumes for the ions (MARSDEN, 1963).

III. *K^{42} and Na^{24} in the instilled volume during secretory arrest.*

These experiments show that diffusion from the stomach is a rather slow process with less than 40 % disappearance of the specific activity from the instilled volume in an hour. The observation that the K^{42} activity disappears somewhat faster than Na^{24} from the stomach supports the hypothesis that K^{42} equilibrates with a mass of potassium larger than the Na pool available for Na^{24} equilibration. This must mean that the K^{42} passes largely into the intracellular space. (This is in accordance with the conclusion that potassium to a certain part exchanges with the intracellular space in the cells in the stomach mucosa via the crypts.)

General Summary

The aim of the investigation was to study the kinetics of volume secretion and ionic transport rate (H^+, K^+, Na^+ and Cl^-) in the intact stomach of man and dog. Especial emphasis has been placed on the $[H^+]$ and $[K^+]$ relationships.

Procedure

Human subjects and dogs with gastric fistulae were used. A steady gastric secretion rate was induced by the continuous intravenous injection of histamine. An antihistamine (chlorpheniramine) was given before the injection of histamine in order to reduce its side effects. The bidirectional movements of potassium and sodium were also studied with the use of radioisotopes. These experiments were performed on dogs and cats mostly under general anaesthesia.

Methods of analysis

The methods used are described in the text in connection with the relevant chapters. They include the following analyses: (1) acidity; (2) pH; (3) chloride; (4) sodium and potassium; (5) radioactive sodium and potassium.

The relationship between the injection rate of histamine and rate of gastric secretion

The importance of steady state conditions during stimulation is stressed. The relationship was found to be well described by an exponential equation as proposed by Öbrink (1948). It was shown that the antihistamine (chlorpheniramine) had no effect on the gastric secretion. Three parameters describing the relationship between the rate of secretion and the dose of histamine were determined and dis-

cussed. They were: the maximal rate of gastric secretion, the sensitivity of the mucosa to stimulation and the basal secretion. An "approximation" test, for a more rapid estimation of the parameters mentioned, is described.

In man a basal secretion was always observed, but this could not be conclusively demonstrated in dog. The initial slope of the rate of volume secretion as a function of the rate of histamine injection was proposed as a measure of the sensitivity of the gastric mucosa to histamine stimulation and thus should give additional information concerning *hyper-* or *hypo*secretion of gastric juice.

The relationship between the acidity and rate of gastric secretion

The experimental data fitted well the concept of a diffusion-like process as the main factor for the acidity regulation. The amount of "bound acidity" was observed to be almost negligible. Quantitatively the same relationship was found to be valid in man and dog. On theoretical grounds different relationships between acidity and rate of gastric secretion can be expected, if different degrees of mixing between the newly formed gastric acid and the preexisting gastric contents occur.

The experimental results indicated that normally the mixing is somewhat incomplete. *The primary acidity in man was found to be lower than in dog.* No evidence was found for other mechanisms that secondarily might lower the acidity in man and the difference in primary acidity in man and dog was considered to be real.

An "approximation" test to evaluate the acidity–secretion rate relationship more rapidly with a graphical method was described and carried out.

The permeability coefficient, k, was proposed as a measure of a possible *hyper-* or *hypo*acidity.

The relationship between $[Cl^-]$ and rate of gastric secretion

This relation was found to be quantitatively the same both in man and dog. The sum of $[K^+]$, $[Na^+]$ and $[H^+]$ was equal to $[Cl^-]$. $[Cl^-]$ in the "primary secretion" was calculated with a graphical method and found to be similar in man and dog.

Relationship between [Na^+] and rate of gastric secretion

The same quantitative relationship was found in man and dog. The data fitted reasonably to a hyperbolic regression equation, derived from the diffusion hypothesis. The results do not contradict the assumption that there is no sodium in the "primary secretion".

The relationship between [K^+] and rate of gastric secretion

During a steady rate of gastric secretion [K^+] was observed to be fairly constant. A straight line relationship was found to fit the experimental data rather well both in man and dog. An essential difference between man and dog was found. With increasing rates of gastric secretion [K^+] increased in man. In dog [K^+] remained about the same concentration at different secretory rates. At very low rates of secretion [K^+] tended to be the same in man and dog. The K^+-content in the gastric secretion was concluded to be dependent on the secretory process.

The lower primary acidity in man corresponded with a higher [K^+] than in dog, so that the sum of [H^+] and [K^+] in the primary secretion was similar in man and dog. It was proposed that K^+ in the gastric secretion was partly of intracellular origin.

The effect of histamine on plasma [K^+]

It has been reported that histamine liberates potassium from body tissues (e.g. MacMillan *et al.*, 1956). The importance of these findings were investigated in order to assess their possible significance with regard to the differences in [K^+] in gastric secretion between man and dog. Comparison of plasma [K^+] before and during histamine administration (*in vitro* and *in vivo*) showed no significant evidence of increase in plasma [K^+] with histamine administration. The conclusion was drawn that [K^+] in gastric secretion depends on some local process in the mucosa.

Analysis of the fluxes of K and Na in the stomach

The specific activities of potassium and sodium were measured in plasma and gastric contents during steady gastric secretion and during secretory arrest.

During secretion the intravenously injected K^{42} and Na^{24} were found to exhibit a peak value in the gastric secretion. After the peak the specific activity of potassium was found to be considerably lower at the same time as the specific activity of sodium was almost the same as in plasma.

When K^{42} and Na^{24} were given intravenously during secretory arrest only part of the sodium activity and almost none of the potassium activity had passed into the stomach after an hour.

During secretory arrest with the isotopes instilled in the non secreting stomach the specific activity was found to decline by 23–36 % in an hour with a tendency for potassium to disappear a little faster.

To explain these results *it is proposed that potassium in the gastric secreton orginates at least partly from the intracellular space in the gastric mucosa.*

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